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The National Children's Study: How obstetricians can contribute

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Abstract

The National Children's Study is an observational prospective cohort study that is designed to assess the multiple factors that can affect pregnancy outcomes and children's development. It promises to overcome the limitations of previous observational studies with regard to sample size (105,000), generalizability, breadth of environmental exposures, and the time frame of follow-up (21 years). As gynecologic and obstetric care providers, we have an integrally important role in facilitating the success of the NCS. This article enumerates the multiple ways in which we can be of invaluable assistance.

Keywords

National Children's Study; obstetricians; review

The rationale for The National Children's Study

As obstetricians, we are all aware of the multiple factors that can affect pregnancy outcomes. One need only consider preterm delivery to understand the multiplicity of exposures that may contribute to an adverse obstetrical event. Genetic predispositions, inflammatory mediators, and social conditions all have been implicated as factors underlying preterm birth.^{1–4} Moreover, because preterm birth is such a major contributor to neonatal mortality and morbidity, it is clear that many exposures contributing to adverse obstetrical outcomes also contribute to worsening health and welfare of our children, and ultimately, our entire society.⁵

Preterm birth is one of the most overt examples of the relationship between pregnancy outcomes and child health. At the time of a preterm birth, there is immediate evidence that an adverse obstetrical outcome has occurred; after the preterm birth, there is commonly a clear link between the gestational age at birth and the pediatric health sequelae, whether immediate (e.g. intraventricular hemorrhage) or long-term (e.g. cerebral palsy or developmental delays). Yet, there has been increasing evidence that the health of children, and the adults that they will become, is dependent upon multiple other pregnancy-related events and exposures, many of

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which are more subtle, and some of which may not even be recognized as “adverse”, at the time they occur. The “Barker Hypothesis”, for example, posits that *in utero* exposures can affect physiology for the rest of an individual’s life, influencing risk for developing cardiovascular morbidity, obesity, diabetes and other diseases.^{6–9} Neurodevelopmental disability and mental illness are also thought to have origins during fetal life.^{10,11}

Despite an understanding of the general association between maternal and child health, the importance of specific exposures during pregnancy on different aspects of child health remains poorly understood. This lack of understanding can be linked to the sheer number of exposures and influences that need to be considered and assessed. Environmental and chemical exposures, genetic differences, biological factors, and the cultural and social milieu of a family all contribute to children’s health. Investigators who attempt to assess the relationship between even one of these factors and long-term health outcomes are faced with enormous operational and financial challenges; the challenges for those trying to account for the complex interactions and contributions of all of these factors are multiplied further. And, even when multiple factors have been assessed, it has often been among populations of relatively small sizes and of specific regions, limiting the capacity to examine less common outcomes and the ability to generalize any findings to the wider society.

Thus, at this point in time, it is evident that (1) obstetrical, *in utero*, influences are fundamentally important influences upon the health of our children and society; (2) *in utero* effects are modified by the influences of postnatal life; and (3) the true association of genetic and environmental influences during pregnancy and the postneonatal period with health outcomes can only be established with a study that comprehensively and systematically collects exposures as well as short and long-term health outcomes. The Eunice Kennedy Schriver National Institute for Child Health and Human Development has designed the National Children’s Study (NCS) to enable the assessment of these varied and complex associations.^{12,13}

What is the National Children’s Study?

The NCS is an observational prospective cohort study that is designed to overcome the limitations of previous observational studies with regard to sample size, generalizability, breadth of environmental exposures, and the time frame of follow-up. First, with regard to sample size, the study aims to include 105,000 children from across the country. With this large study population, relatively rare exposures as well as rare outcomes will be assessed and evaluated. As for generalizability, the study was designed to be nationally representative with a probability-based sampling approach and includes the diverse populations represented in the US. Study participants will be recruited from among the 105 study locations that represent a geographical cross-section of the United States.

The study is also designed to evaluate multiple different environmental exposures and influences. “Environment” is defined broadly, and is considered to include the many influences that may affect children’s health. These influences include exposures that occur both before and after birth. In addition, environment includes influences that are “internal” (e.g. biologic and genetic influences) and “external” (e.g. chemical exposures, physical surroundings, and social factors) to an individual.

Samples, interview data and measurements will be collected during a preconception visit (if possible), during each trimester of pregnancy, at birth and multiple points following birth. The samples and information to be collected reflect the breadth of influences that can be evaluated. With regard to parental exposures, in-person interviews, self-administered questionnaires, and diaries are all going to be completed and allow the assessment of life events, daily exposures, medical access, and an individual’s social milieu. Environmental samples, including air, dust,

water, and soil specimens are going to be collected from the parental home. Maternal biologic samples will include blood, vaginal swabs, urine, saliva, hair, and nail clippings. For a subset of women, samples will be collected even before pregnancy is conceived. During pregnancy, in addition to the aforementioned samples being collected, mothers will undergo three ultrasound examinations; and after delivery, samples of umbilical cord blood, meconium, and the placenta will be collected. Even community-level assessments, such as food samples, child care locations, and neighborhood evaluations are planned. And, of course, since this is a study of children's health, biologic samples and physical examinations will also be obtained from the child after birth.

The length of time that each child will be followed is another distinguishing characteristic of the study. Children's health outcomes will be determined through 21 years of age. This long-term follow-up optimizes the chance that primary health outcomes can be ascertained, and that the association between exposures and outcomes at many different times of development can be evaluated. Indeed, repeated samples and data collection are planned throughout pregnancy and post delivery, allowing not just the exposure, but the timing of the exposure to be reliably assessed. And, since the study is prospective in nature, a temporal relationship between exposure and outcome, with a reduced contribution from recall bias, will be able to be determined.

What hypothesis will the National Children's Study test?

It is not hard to imagine the many different hypotheses that could be tested by a study that follows 100,000 children over 21 years, and has exposure data for these children that spans preconceptional, prenatal, and postnatal time frames. In fact, one of the advantages of this study is that, given the banking of specimens that will be performed, even questions that only become apparent in the future, as further scientific investigations occur, will still be able to be evaluated. Nevertheless, multiple hypotheses have already been formed and will be able to be tested from the data collected in the NCS. Some of these analyses are concerned with exposures that occur and outcomes that manifest only during postnatal life. For example, the cognitive development of children will be evaluated in the context of their interaction with different types of media, the presence of and relationships with social institutions in their community, and pesticide exposure. The development of asthma will be explored in relation to dietary antioxidants, indoor air pollutants, and early exposure to microorganisms. Obesity, a public health problem that has reached epidemic proportions, will be assessed in regard to breastfeeding and childhood glycemic loads.

Nevertheless, some of these outcomes may have antecedent contributions from exposures that occur during the prenatal period, when we, as obstetricians, are caring for both the mother and her fetus. Prenatal infections, for example, will be assessed for their association with neurodevelopment disabilities such as cerebral palsy, autism, and schizophrenia. Additionally, the development of asthma will be explored as a function of maternal stress, while the development of obesity will be explored as a function of impaired maternal glucose metabolism. The discovery of these associations may provide direction for interventions in obstetric care that could affect children for years and perhaps the entirety of their life.

Moreover, some of the hypotheses to be evaluated have implications not only for altering the care we provide, but also for the adverse obstetric outcomes that we have struggled to reduce. Thus, in addition to the above noted pediatric outcomes, glycemic control, even in non-diabetic women, also will be evaluated for its association with major congenital anomalies. Preterm birth, the greatest cause of neonatal mortality in non-anomalous fetuses and an adverse event with a significant racial disparity, will be assessed in relation to multiple mediators and sources of inflammation, as well as the presence of a conception achieved through assisted reproductive

technology. In addition, the association of assisted reproductive technologies with a host of outcomes, including intrauterine growth restriction and neurodevelopmental disabilities, will have the potential to be evaluated.

What can we do, as an obstetric community, to make the National Children's Study a success?

As gynecologic and obstetric care providers, we have an integrally important role in facilitating the success of the NCS. Given the wide range of geographic locales from which patients will be sampled, many of our patients will have the opportunity to be involved in the study. There are several ways to help facilitate participant enrollment and successful collection of data and specimens for enrolled participants (see Table 1). Although women will be contacted to participate by NCS personnel, women's general knowledge of the study, as well as the support of their health care providers, may be critical factors in determining whether they will choose to participate. Also, there may be the opportunity to enroll patients within provider offices. Correspondingly, providers who are in communities where NCS recruitment will occur could work with the NCS Center that is responsible for the local management of the study. Helping to publicize the presence of the NCS in the community and the importance of the NCS for children's health will be extremely valuable. Also, when patients ask about the NCS, having general knowledge of the overall methods and aims, as well as communicating general support for participating in the study may be important determinants in their decision to enroll.

Once participants are enrolled, the National Children's Study personnel ultimately will be responsible for organizing and completing specimen collection. Nevertheless, as this collection will occur in multiple clinical areas, including ultrasound suites, outpatient examination rooms, and hospital rooms, our role in supporting data and specimen collection is an important one. When necessary, working with NCS personnel to facilitate staff acceptance and integration within our ambulatory settings for scheduled data and specimen collection is critical to successful protocol completion. Specimens collected at or immediately after delivery have the added challenge of an event with unpredictable timing. For deliveries, recognizing that our patient is in the NCS is important to the success of the study; we need to be aware that NCS personnel (if they have not already been notified) should be alerted to the participant's impending delivery, and that relevant specimens (such as placenta) should be collected.

The NCS promises to be one of the most important endeavors in establishing the seminal environmental influences that affect children's health. The NCS has implications for our fundamental understanding of human development, for our prioritization of public health initiatives, and for the clinical medicine that we practice. For our patients, it holds the promise of elucidating a multitude of factors that can be utilized to improve their health outcomes. Ellen Goodman has written that, with regard to children, the central struggle is "to let our hopes outweigh our fears." The NCS is an attempt to further and better identify the exact nature of what it is that we do need to fear in order that our hopes for our children, and our society, can be fully realized. Those who wish to learn more about the Study and determine if their communities have been selected for enrollment should visit the National Children's Study website at www.nationalchildrensstudy.gov.

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Table 1

How gynecologic and obstetric providers can help make the NCS successful

Help publicize the study to our patients
Understand the importance of the study for our patients and our communities
Facilitate patient recruitment in conjunction with the local National Children's Study center
Support the decision of our patients to participate in the study
Work with the local National Children's Study center to facilitate and achieve the collection of obstetrically-related biological samples from enrolled participants