National Children's Study Assembly
Breakout Session: Pregnancy Outcomes, Growth, and Physical Development
November 29, 2005
Omni Shoreham Hotel
Washington, DC

This meeting was held in conjunction with the National Children's Study, which is led by a consortium of federal agency partners: the U.S. Department of Health and Human Services (DHHS) (including the National Institute of Child Health and Human Development [NICHD] and the National Institute of Environmental Health Sciences [NIEHS], two parts of the National Institutes of Health, and the Centers for Disease Control and Prevention [CDC]), and the U.S. Environmental Protection Agency (EPA).

Co-Chair: Kenneth C. Schoendorf, M.D., M.P.H., Member, Interagency Coordinating Committee; National Center for Health Statistics, CDC, DHHS

Co-Chair: Adolfo Correa, M.D., Ph.D., Member, Interagency Coordinating Committee; Medical Epidemiologist, National Center on Birth Defects and Developmental Disabilities, CDC, DHHS

Invited Participant: Donald J. Dudley, M.D., Department of Obstetrics and Gynecology, University of Texas Health Sciences Center; Member, Federal Advisory Committee

Invited Participant: David J. Schonfeld, M.D., Division of Developmental Disabilities, Cincinnati Children's Hospital Medical Center; Member, Federal Advisory Committee

Invited Participant: Mary Hediger, Ph.D., National Institute of Child Health and Human Development, NIH, DHHS

Welcome, Introductions, and Purpose of Session

David J. Schonfeld, M.D., Division of Developmental Disabilities, Cincinnati Children's Hospital Medical Center; Member, Federal Advisory Committee

Dr. Schonfeld welcomed participants and said that the goal for the session was to provide an opportunity for investigators and other participants to learn about plans for proposed methods of assessing pregnancy outcomes, especially birth defects, and physical development for the National Children's Study; to ask questions; and to provide input on selection of methods.

Dr. Schonfeld introduced himself and stated that growth and body composition, both fetal and infant, and the presence and nature of birth defects are essential outcome measures for the National Children's Study. In addition, measures of growth relate to many of the Study's central hypotheses and represent potential mediating variables of interest, measures of susceptibility to adverse influences, or early markers of adverse outcome. So therefore it is very important that the Study selects measurement methodologies that are sensitive, reliable, valid, and feasible.

He provided a brief introduction to the session's agenda and the other presenters. The agenda included overviews of two Study workshops held in the fall of 2004:

- The Assessment of Growth and Body Composition Workshop (October 7–8, 2004)
- The Ascertainment and Diagnosis of Birth Defects Workshop (October 18–19, 2004).

Posters about the two workshops were available for viewing following the breakout sessions.

Dr. Schonfeld noted that there would also be a time for questions and a summary at the end of the session.

Findings from the Assessment of Growth and Body Composition Workshop

Mary Hediger, Ph.D., National Institute of Child Health and Human Development, NIH, DHHS

Dr. Hediger noted that the workshop report is available on the Study Web site at: http://www.nationalchildrensstudy.gov/events/workshops/growth-body102004.cfm. She explained that the workshop grew out of the work of the Nutrition, Growth, and Pubertal Development Working Group, which she co-chaired with John Himes. A subcommittee was tasked with developing a framework for the measures to be considered in the workshop.

Primary objectives for the workshop were:

- To assess methods (how good) for measuring growth and body composition
- To determine appropriateness (how useful) of measures for Study use
- To pay attention to concordance between prenatal and postnatal measurements.

Secondary objectives included the following:

- To recommend a schedule for timing of collection (chronological or gestation-corrected ages)
- To recommend concurrent measurement of biomarkers (or collection of biospecimens) for interpretation, diagnosis, or prediction
- To recommend protocols for ensuring the standardization of measurement (technicians), instrumentation, and quality control
- To recommend pilot studies for instrument validation, to provide more accurate equations, and to identify promising new techniques.

Dr. Hediger reviewed the conceptual framework for determining assessment measures related to growth and body composition, which included consideration of (1) appropriateness for the Study, based on criteria such as relevance to Study hypotheses (such as those related to gestational diabetes, asthma, and obesity), safety, and minimal burden; (2) feasibility and applicability (survey and laboratory methods); and (3) technical issues, including those related to precision and validity, technicians and training, standardization, and quality control. The workshop planners were also interested in whether measures should be recommended for use in the entire sample or in a subsample.

Dr. Hediger presented information about three classifications of measurements defined in the workshop, which include "field" methods, laboratory methods, and laboratory "plus" methods.

- **Level 1—Field Methods:** These methods are reliable, widely-used, inexpensive, and relatively safe and can be used to measure all participants at all ages. These are core measures. Examples include anthropometry, two-dimensional (2D) ultrasound for fetal biometry, quantitative ultrasound, and bioelectric impedance analysis (BIA).
- **Level 2—Laboratory Methods:** These methods are more precise, but more expensive, less safe (due to radiation exposure, for example), and more burdensome. One concern is that use of these methods would require a primary data repository and probably centralized evaluation or reliability oversight. They might be used on all subjects but would most likely be used with subsamples, and core measures (field methods) would still be needed for continuity. Examples include three-dimensional (3D) ultrasound, dual-energy x-ray absorptiometry (DXA), air displacement plethysmography, total body electrical conductivity (TOBEC), indirect calorimetry and fat oxidation, and various tracer dilutions.
- **Level 3—Laboratory Methods Plus:** These methods are extremely precise but are the most expensive, least safe, and most burdensome methods. A primary data repository and centralized evaluation or reliability oversight would be needed. The methods would be used only in subsamples to address specific hypotheses (certainly not in all ages) or to validate Level 1 and Level 2 measures or in pilot studies. Examples include whole body magnetic resonance imaging (MRI) and computed tomography (CT).

The workshop structure was organized by life stages (pregnancy, fetal growth, birth to age 3, children 4–9 years, adolescents 8–18 years) and by body compartments (fetal body composition, lean body mass (LBM), body water, skeletal muscle mass, bone mineral content and density, adiposity and regional fat distribution, and biomarkers of obesity).

Dr. Hediger summarized the information requested of each life stage group of workshop participants: measurements (level 1, 2, and 3) and rationale, technical concerns, concurrent measurements that should be taken, and pilot or validations studies needed.

Results of the workshop included charts (presented by Dr. Hediger) that indicated recommended measurements in pregnancy, fetal growth measures, and measures in neonates to age 3 years, including dimension, methods, and timing. These may be found in the workshop summary on the Study Web site, as noted.

Recommendations for pilot or validation studies that emerged from the workshop included the following:

- Measurements in pregnancy
  - Subcutaneous fat measurement with Lipometer® requires more study, validation
  - Body water BIA requires validation of equations
  - Regional fat mass—new DXA algorithms for visceral fat
  - Consider regional quantitative ultrasound for bone density
- Fetal growth measurements
  - Subcutaneous fat measurement on 2D ultrasound needs standardization
  - Use of 3D ultrasound for biometry needs to be assessed and methods of measuring organ/limb volumes standardized

- Neonates to age 3 years
  - Circumferences and regional fat measurements (DXA) need standardization
  - Arm span only when stature not feasible.

Discussion

Questions and comments concerned the following topics:

- *Whether CPK would be evaluated in the blood of newborns.* Dr. Schoendorf responded that while cord and newborn blood will be taken, exactly what will be analyzed has not yet been decided.

- *Inclusion of maternal blood pressure in the Study.* Dr. Hediger replied that the workshop did not address blood pressure, but maternal blood pressure will certainly be part of the Study and will be measured at every prenatal visit.

- *How the Study will get women to come in when they are not scheduled to come in. Women do not know they are pregnant in the earliest stages of pregnancy*. Dr. Hediger replied that the only measurement that was specifically recommended for the first month of pregnancy was ultrasound dating and that 25 percent of women will be enrolled preconceptionally. Dr. Dudley commented that this issue will be addressed through recruitment and retention strategies.

- *The strength of science-based support for biomarkers.* Dr. Hediger responded that the workshop did not address biomarkers specifically and was focused more on measures of growth than on other kinds of adverse outcomes.

- *Measures of growth velocity.* Dr. Hediger said that it would depend on the protocol and timing of the measurements and noted that certain more intensive measures may be done at various centers.

- *Notation of drugs that the fetus is exposed to intrapartum.* Dr. Correa said that another group is looking at measures of exposures in pregnancy and will also look at intrapartum exposures.

- *Distinction between babies small for gestational age versus fetal growth restriction.* Dr. Schoendorf said that the Study will have reasonable measures related to gestational age and birth weight, and in addition, it will have serial measures of fetal growth during pregnancy. Dr. Hediger added that most major medical centers would do physical profiles and tests as standard care, even if they are not part of the protocol.

- *PEAPOD.* A participant commented that the PEAPOD method is being used.

Findings from the Ascertainment and Diagnosis of Birth Defects Workshop

Adolfo Correa, M.D., Ph.D., Member, Interagency Coordinating Committee; Medical Epidemiologist, National Center on Birth Defects and Developmental Disabilities, CDC, DHHS

Dr. Correa explained that the motivation for this workshop stemmed from a core hypothesis that among women without diabetes before pregnancy, impaired glucose metabolism during pregnancy is associated with major birth defects in their offspring. An earlier workshop held in December 2002 concluded that there were major challenges in ascertaining and diagnosing birth defects in a longitudinal study such as the National Children's Study and found that no standard methodology was available. A second workshop was then planned.

Workshop objectives were:

- To identify methods for ascertaining birth defects *in utero*, in infancy and in childhood
- To identify possible pilot studies for assessing feasibility, reliability, and validity and for standardization of ascertainment methods.

The workshop included presentations on lessons learned and new methods, including prenatal ultrasound exams, examinations of fetal deaths, prenatal and postnatal exams for heart defects, and new technology for evaluation of facial features in children using 3D photographic imaging.

Dr. Correa explained that workshop participants met in four breakout groups, which addressed the prenatal period, fetal deaths, cardiac defects, and other defects. The groups were charged with identifying methods, timing, and related issues (such as feasibility, burden, costs, and technical issues) as well as the appropriateness of methods for the whole Study or for substudies. The groups were also asked to identify possible pilot studies needed.

Prenatal Period Group. The prenatal period group participants identified maternal blood samples and 2D ultrasound as the more feasible methods and noted that attention should be paid to quality control issues for 2D ultrasound. Methods considered less feasible for the Study were 3D ultrasound and MRI; however, the group noted that these might be useful in specific situations.

Fetal Deaths Group. The fetal deaths group identified the need to conduct external and internal exams, digital photography, and chromosomal analyses to ascertain and document the presence of birth defects. Participants noted that the potential for obtaining useful information would depend on the availability of expertise to conduct the exams at the sites, the gestational age, and the condition of the fetus or stillbirth. Possible protocols suggested included:

- The development of a standard postmortem exam
- The inclusion of such an exam as part of a standard protocol to determine conditions associated with fetal losses and infant and child deaths
- The development of a standard protocol for examination of all placentas.

Heart Defects Group. The heart defects group identified the need to obtain family and child history and exam of the child at every visit. Other methods identified included:

- Fetal echocardiogram and 2D echocardiogram at birth and 14 years, with concerns about needed expertise, false positives, and costs
- Pulse oximetry at 24–36 hours of age, with concerns about false negatives
- Electrocardiogram (ECG) at 6 years, with concerns about inter-rater reliability.

Other Birth Defects Group. The group considering other birth defects suggested three types of examinations/methods:

- A standardized medical history of the mother prenatally and of the newborn at 1–3 days of age
- A dysmorphologic exam at 1–3 days of age and every 5–7 years
- Standardized 2D photos of the face at 1 and 3 years.

Training of personnel and standardization of the exams and photos were the main issues identified. For ascertainment of birth defects in infants and children, it was suggested that two basic protocols be developed: one for training personnel to conduct structured dysmorphologic examinations, and another for one for the definition of criteria and procedures for referral to dysmorphologists for additional investigations.

Dr. Correa presented a table summarizing the possible examinations suggested by the workshop participants for ascertaining birth defects by lifestage; the table was included as part of the poster about the workshop in the poster session. He noted that the full workshop report is available on the National Children's Study Web site at: http://www.nationalchildrensstudy.gov/events/workshops/ascertainment_102004.cfm.

Dr. Correa described a possible clinical evaluation at birth that might include a review of prenatal records, the family history, an exam, photographs, and pulse oximetry. Findings might then lead to an echocardiogram, cytogenetics, or placental pathology, and an autopsy might be performed in the event of stillbirth.

Questions that remain include:

- How can such an approach be translated into a practical and useful algorithm in the Study, considering burden, costs, and feasibility?
- Which components of the birth defect evaluation are part of the Study and which are part of standard clinical care?
- How should birth defects/syndrome diagnoses be classified and coded?
- What pilot studies are priorities?

Discussion

Questions and comments from session participants concerned the following topics:

- *The process for how the Study protocol is being developed.* Dr. Correa explained that the process will be defined over the next few months, and a draft protocol is expected in February.

- *Approach to fetal deaths.* Dr. Correa said that the suggestion for a postmortem exam was made in the context of what investigators would want, but the exam has been a challenge in other investigations. Dr. Dudley commented that there could be 500 stillbirths with autopsies over the course of the Study and a standardized approach would be needed with the large number of Study sites. Dr. Schonfeld suggested that offering the postmortem exam to all families as a service was an effective approach; one should not assume that families will reject the exam. Dr. Dudley noted that community hospitals might not offer that opportunity.

- *What the Study will assay in maternal blood, such as biomarkers for inflammation.* Dr. Dudley said that this is a key facet of the Study and there will be several sampling timepoints. Issues will be sample volume and what will be assayed.

- *Whether fetal deaths would be considered part of the 100,000 participants or whether they would be replaced by live births.* Dr. Dudley replied the Study population will include 100,000 live births, and sampling will continue until that target is reached. Dr. Schoendorf said that sampling is based on the estimated number of households needed to yield the number of women of childbearing age and the total number of children; thus, the fetal death rate and stillbirths are factored in ahead of time.

- *Use of modern fertility technology.* Dr. Dudley responded that the Study has been charged to oversample that population in response to a request by the President's Task Force on Bioethics.

Summary

Donald J. Dudley, M.D., Department of Obstetrics and Gynecology, University of Texas Health Sciences Center; Member, Federal Advisory Committee

Dr. Dudley noted that Study workshops bring together "the best of the best" to inform policy for the Study. An enormous amount of brainpower has been expended on behalf of the Study. Workshop participants are asked what they would want to study in an optimal situation—so that is what comes out of the workshops. However, the Study's budget may not allow all desired tests, and subject burden is a major issue. Dr. Dudley noted that this is a particularly exciting time as the Study moves from concept and study design into the protocol and implementation phase.

Regarding the workshops, Dr. Dudley said that many measures have not been standardized and validated in a large population. Regarding intrauterine growth restriction and birth weight, the sample size will allow a continuous variable. He asked Dr. Schoendorf to comment about a feasibility study of 3D ultrasound.

Dr. Schoendorf explained that there was a Study workshop on fetal growth assessment that produced a recommendation for the use of 3D antenatal ultrasounds. However, a pilot test in three sites produced data that, although not yet formally analyzed or peer reviewed, indicate that the technology is not quite ready for use in a multisite large study such as this one. A

standardized protocol had to be developed for the pilot study that required a considerable amount of training and retraining to follow. The pilot study found problems with low concordance between readings at different sites and significant burden issues for the researchers.

Dr. Dudley mentioned that the same could be said about fetal echocardiograms and commented that autopsy would be needed not only in the case of stillbirth, but also in the case of any infant death, especially those associated with congenital anomalies. Dr. Correa said that the birth defects workshop participants did suggest coming up with a protocol for doing a postmortem exam not only on fetal deaths but also on infants and children who die during the Study.

Discussion

Session presenters responded to questions and comments from participants concerning the following issues:

- *Provisions for subjects' mothers who die during the Study*. Dr. Dudley said that few would be expected to die from pregnancy-related complications, so that will be a small population. Cancer is a similar situation—even with 100,000 subjects, the population will not be large enough to tell much, and the same is true with maternal deaths.

- *Measurement of alcohol and drug abuse in pregnancy.* Dr. Schoendorf asked whether the question was about the measurement of those issues or the responsibility of the Study to act in the case of less than optimal situations. He noted that those types of exposures are important and those types of measures are being addressed. Dr. Dudley said probably this would fall in the chemical exposures area. The ethical and moral issues associated with identifying children affected by such exposures are recognized as very important. Ethical issues weigh heavily on the Federal Advisory Committee and its Ethics Subcommittee—for example, the responsibility of the Study versus the responsibility of the caregivers and issues of confidentiality.

- *Tracking the health of the 100,000 mothers of the Study participants.* Dr. Correa said that the framework of the Study is to look at families, including parents and maybe siblings of participants, and that this is an important question. Dr. Dudley said that the long-term health of the mother certainly has an impact on the health of the child. Dr. Correa noted that the Social Environment Working Group had emphasized issues of this nature.

Additional Participants

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