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Eunice Kennedy Shriver National Institute of
Child Health and Human Development
Scientific Vision Workshop
on Pregnancy and Pregnancy Outcomes

February 22–23, 2011
Bethesda, Maryland

Workshop White Paper

by Workshop Organizers:
(in alphabetical order, by role)

Patrick M. Catalano, M.D. (Co-chair)
Case Western Reserve University

Michelle A. Williams, Sc.D. (Co-chair)
University of Washington

Paul H. Wise, M.D. (Co-chair)
Stanford University

Diana W. Bianchi, M.D.
Tufts University

George R. Saade, M.D.
University of Texas Medical Branch

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INTRODUCTION

Ensuring healthy childbearing and birth outcomes remains a central challenge to the medical research community and must represent a core responsibility of the NICHD. More than 85% of all women will experience pregnancy sometime in their lives and its influence on a woman's health and well-being over the lifecourse can be profound. The scale of adverse birth outcomes in the United States remains greater than in other industrialized countries, and the impact of these outcomes ripples across the full epidemiology of childhood. Moreover, despite years of directed research and public concern, disparities in maternal health and birth outcomes have only grown over the past decade (Alexander et al., 2008; IOM, 2006; Wise, 2004).

Both the complex biologic nature of pregnancy and its sensitivity to dynamic social forces suggest that traditional, isolated arenas of research will not likely generate the investigative insight or practical interventions so urgently needed by the clinical and public health communities. Rather, new research strategies will be needed to organize and facilitate collaborative approaches that can transcend traditional disciplinary boundaries and create new, more creative pregnancy-related science. Simply put, the complexity of pregnancy and birth demands more than the status quo is likely to provide; new, far more innovative research strategies are required.

This white paper summarizes the findings of a workshop explicitly organized to address this challenge. The mandate and structure for the conference as well as the expertise of the invited participants were all developed to generate highly interactive discussion and innovative recommendations. The workshop participants were organized into seven groups, each focused on a specific arena of pregnancy or birth outcomes, e.g., 1) New Methodologies; 2) Balancing Maternal and Fetal Risks and Timing of Delivery; 3) Preventing Cesarean Deliveries; 4) Pregnancy and Future Health; 5) Prenatal Diagnosis; 6) Placental Medicine and Syndromes; and 7) Preterm Birth.

In order to attend to the central mandate for cross-disciplinary interaction, each group was comprised of experts from a variety of disciplines. These disciplines included basic scientists, placental biologists, microbiologists, endocrinologists, epidemiologists, obstetricians, maternal-fetal obstetrical specialists, and pediatricians. A special effort was made to ensure that expertise in the basic, social, and clinical sciences was represented in each of the specified groups. Group leaders explicitly facilitated deliberations to generate intense, interdisciplinary interaction. In addition, plenary sessions brought together all the groups and engaged participants in common discussion and critical interchange.

What emerged from the workshop was a general consensus that a restructured and re-energized research initiative was needed. This took the form of four general themes as well as a series of specific recommendations. The general themes reflected both the comprehensiveness and the boldness of the mandate to the workshop and were articulated as: understanding the biology of pregnancy, applying biology in clinical situations, viewing pregnancy as a lifecourse event, and developing the tools that will be needed to advance research.

These broad considerations reflect the need to develop new scientific insights and the translational mechanisms that will ensure that new scientific discoveries are transformed into effective interventions that are equitably accessible to all women and children in need.

COMMON THEMES

UNDERSTANDING THE BIOLOGY OF PREGNANCY

As suggested above, knowledge is a critical driver of medicine and health. Workshop participants identified insights into the biology of pregnancy as an important priority of future research. In particular, groups emphasized the importance of enhanced understanding in the following areas: 1) the fundamental processes that underlie embryonic development, 2) the function of the placenta in maternal-fetal crosstalk, 3) maternal adaptation to pregnancy, and 4) the biological definition of an optimal pregnancy phenotype from the fetal, maternal, or paternal standpoints.

These insights will lead to better definitions of a “normal pregnancy” and the deviations that constitute disease.

Progress in the field will be markedly accelerated by improvement in measurements of normal fetal development and maternal physiological adaptation, and assessment of physical, chemical, nutritional, and microbial exposures—the exposome—and their relevance in the context of disparate social environments (see discussion of “exposome” in the “Pregnancy is a Lifecourse Event” section below).

It is crucial that investigators remember that unlike other physiological or pathological states, the biology of pregnancy involves more than a single human organism, and these multiple organisms might have compatible or conflicting interests. Further, each organism interacts with a non-uniform exposome.

Whereas the biology of the fetus, placenta, and mother each can be studied independently, future research should strive to integrate knowledge in these central components and create a network of players at multiple levels, including genes, molecules, cells, tissues, organisms and the environments in which they live. Data about these harmonized, pregnancy-centric biological networks (“gestome”) can be combined with medical and social information in order to fully understand gestational health. It is clear that well-designed mechanistic experiments using mice and other relevant animal models will be pivotal in analyzing these biological networks and deciphering the full impact of disease-causing perturbations. Such integrated networks can become useful tools to study not only physiological and pathological processes, but to truly assess diagnostics, prediction, therapy, and prevention, which will be corroborated by clinical trials. Developing means for providing methodological and logistic support for perinatal research, following the CTSA model, would be particularly helpful in this regard.

APPLYING BIOLOGY IN CLINICAL SETTINGS

There is a critical need to develop methods to serially and non-invasively screen for various antepartum and intrapartum complications. Screening would help predict which patients are at risk for developing complications, diagnose, and better categorize the conditions. As an example,

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screening tests to predict preeclampsia would lead providers to check blood pressure more often in women at risk and less often in women not at risk. A method to better diagnose or characterize preeclampsia would allow targeted interventions such as magnesium sulfate or delivery to those at risk.

Related to this, participants consistently suggested the need for better methods to evaluate maternal and fetal well-being. The current methods—fetal heart rate monitoring and ultrasound—have significant false positive rates, which lead to unnecessary intervention. Future work may attempt to improve on current methods by incorporating measurements not previously used, or may lead to new methods, such as measuring metabolites in fetal organs.

The impact of any advance in predictive and diagnostic methods will depend on effective interventions. We need to develop new and more effective maternal and fetal interventions, as most of the current ones are either not effective or have not been adequately tested. For example, interventions for fetuses with growth restriction await clinical trials. Novel intervention methods are also needed to improve outcomes in fetuses with genetic or congenital abnormalities.

Most obstetrical clinical management involves decisions made between the health care provider and the family. Often, the outcomes to be prevented may have conflicting risks and benefits to mother and fetus/neonate. We need to better understand how these decisions are made and how to better weigh outcomes in order to better inform the decisions. We also need to understand the social, behavioral, and systems factors that impact the opinions of the provider and the family.

One important example is the decision regarding whether to deliver a patient or continue with expectant management in the late preterm period. In addition to developing methods to better estimate the risks to the mother and fetus/neonate associated with delivery versus expectant management, it is also crucial to better understand the decision-making process. For example, we need to understand the values patients put on competing outcomes (for example, stillbirth versus neonatal respiratory distress syndrome). We also need better methods to account for competing risks in order to estimate the best timing for delivery. These novel methods may include management algorithms based on decision analyses, cost-benefit calculations, and assessment of impacts on quality of life.

Clinical practice in obstetrics has long suffered from a paucity of high-level evidence to guide it. Investigators could pursue randomized trials to evaluate management strategies for fetal growth restriction, preeclampsia, preterm birth, and fetal therapy. The long-term health of women who have adverse pregnancy outcomes is a recent area of interest that could have significant impact on chronic diseases in adulthood, such as cardiovascular and metabolic diseases. We also need trials to evaluate postpartum management options that could prevent these chronic, long-term outcomes. In addition to randomized trials, observational studies will be needed to inform future trials.

VIEWING PREGNANCY AS A LIFECOURSE EVENT

A classical definition of the lifecourse is “a sequence of socially defined events and roles that the individual enacts over time” (Giele and Elder, 1998). The context of these events is usually

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described in relation to the structural, social, and cultural environment of the individual. Factors such as demography and biology have important roles in defining and influencing the lifecourse. In relationship to pregnancy and pregnancy outcomes, this definition can be easily applied to both the mother and her child.

In the Pregnancy and Pregnancy Outcomes workshop, participants used the term “exposome” (Wild, 2005) to describe the effect of the environment on the developing fetus. This includes not only the environment external to the mother, but the maternal and in utero environments as well. The exposome may have direct effects on structural, genetic, or epigenetic functions of the mother and her offspring. The effects of the exposome may not manifest clinically until after delivery, perhaps not even until childhood or later adulthood. The effects may be as obvious as a structural change or might be more subtle, such as altered metabolic function predisposing to chronic disease. These alterations are not limited to physiological alterations but may include psychological and social adaptations as well, for example, school readiness of the child.

Polling during the workshop revealed that the vast majority of participants believed that the physiological adaptations of pregnancy unmask potential underlying subclinical dysfunction in the mother (94%). However, it seems possible that severe metabolic stress during pregnancy also could contribute to long-term maternal disease.

Currently our understanding of the factors and mechanisms of pregnancy that result in either benefit or harm to the woman and her child are not well understood. The use of alternative models, such as animals and cells, and “omics” approaches can aid us in understanding the mechanisms involved in these biologic processes. Because we also must keep in mind the cultural and social context of these processes in order to maximize the health of the individual, a transdisciplinary approach is necessary.

DEVELOPING THE TOOLS THAT WILL BE NEEDED TO ADVANCE RESEARCH

A basic premise of the workshop’s vision for the future of scientific inquiry into human gestation is that pregnancy and birth outcomes involve highly interactive biological and environmental processes that will not be adequately addressed by the search for singular risks by isolated disciplines. Rather, the outlook depends on an ability to generate research collaborations, integrated datasets, and innovative analytic tools that can begin to bring coherence to complex, intensely interactive etiologic pathways.

Efforts to develop the level of scientific collaboration needed to address these complex challenges have generally taken the form of clustered or “team” science, often involving a variety of disciplines. Many terms have been used to define the structure of these efforts, including multidisciplinary, interdisciplinary, and—more recently—transdisciplinary. Specific definitions for these and related types of investigative interaction vary, but one can summarize the distinctions by the extent to which heterogeneous groups of scholars work side by side (multidisciplinarity), collaborate (interdisciplinarity), or transform one another’s perspectives on a problem (transdisciplinarity).

To create truly transformative transdisciplinary research, funding agencies and academic institutions will need to craft new kinds of collaborative structures and training mechanisms. Of special concern are opportunities for trainees and junior researchers to engage in transdisciplinary team science. Providing such support will require training programs that emphasize the techniques and processes essential to highly interactive, transdisciplinary research. These efforts may also warrant greater collaboration across NIH institutes, particularly when research transcends traditional disciplines or relates to etiologic mechanisms that develop over the lifecourse.

There are also emerging opportunities to craft cross-national research collaborations that take advantage of well-established pregnancy research capacities as well as rapidly expanding activities in parts of the developing world. Highly integrated datasets linking biological, environmental, and clinical attributes could be developed in ways that would not only improve methodologic efficiency and reduce costs but also extend the utility of investigative or evaluative protocols by including diverse populations and groups of investigators. The rapid growth of communications and data-sharing technologies is increasingly making small, highly isolated dataset development obsolete.

The revolution in bioinformatics also is generating remarkable opportunities to conduct innovative transdisciplinary research into pregnancy and birth outcomes. Of special interest is the ability to analyze the large number of relevant datasets that already exist, including those from genomic, proteomic, and clinical studies that are already catalogued for public use. In addition, internet-based consumer activity and social media networks are a potential source of data and participatory research. The challenge lies in generating the questions and methodologies capable of harnessing these data sources as part of a coherent investigative agenda.

New bioinformatics tools could also facilitate the collaborative use of extant biobanks containing samples of animal model or human tissues of direct relevance to the investigation of pregnancy-related processes. Such efforts could help generate greater harmonization of biobanking processes and associated data collection as well as the mechanisms essential to facilitate shared usage and collaborative research.

The emerging understanding of the inherent complexity of pregnancy and childbearing also suggests a need for new analytic models capable of integrating intensely interactive contributors operating over a highly dynamic period of time. In response, there has been a growing recognition that traditional analytic approaches will likely need to be coupled with innovative methods explicitly designed to assess complex physiologic processes and networks of pathologic mechanisms. Advanced analytic methods being developed to address complex systems in other arenas, such as ecology, earth sciences, and physics, could prove increasingly useful in exploring and ultimately addressing adverse pregnancy outcomes.

BREAKOUT GROUP DISCUSSIONS

Breakout Group 1: New Methodologies

The spectrum of events leading from conception to the birth of a healthy infant is both biologically and epidemiologically complex. A simplified time line for the process leading from

conception to birth is shown in Figure 1 (Savitz, 2002) in the appendix. Successful reproduction begins with the first “normal” event, conception, which results from viable sperm reaching the ovum and progressing to implantation. Subsequent normal development depends on differentiation and migration of cells—events that must follow precise timing—leading to the formation of organ systems, and fetal growth and development. Maternal, placental, and fetal problems that arise during pregnancy define adverse outcomes.

The temporal nature of the reproductive process was a recurrent theme of discussion in Breakout Group 1.

First, group members noted that the timing of events is often ambiguous in that some outcomes cannot be observed at the time they are occurring. For example, deviations in placental development early in pregnancy may be important in the etiology of preeclampsia, preterm birth and fetal growth, but these outcomes are identified months later. Furthermore, it was noted that limited access to placental and fetal compartments across gestation complicates efforts to characterize relevant pathophysiological changes across gestation.

Second, pregnancy outcomes such as preeclampsia and preterm birth are complex heterogeneous clinical conditions that should best be studied as homogeneous subgroups. The present reliance on clinical signs and symptoms for defining pregnancy outcomes limits our capacity to define discrete homogeneous outcomes. Characterization of outcomes by objective biochemical and/or molecular signatures of specific pathophysiological processes, for example, may improve definitions of these outcomes.

Third, the low frequencies of relevant exposures (rare exposures), rare outcomes and tendency for the repetitive (high recurrence risk of adverse pregnancy outcomes) across women’s reproductive life requires careful attention to the development of efficient study designs and analytical approaches.

Breakout Group 1 members identified several key methodological opportunities for increasing our capacity for (1) developing clinically useful risk prediction models; and (2) exploring and understanding the etiology of adverse pregnancy outcomes. Improved definitions and measurement procedures of causal factors/clinical risk predictors and outcomes were regarded as fundamental methodological challenges for developing a more robust framework for research in the coming 10 years.

Improved access to well characterized reproductive cohorts (ideally including successive pregnancies of cohort members) with high quality biological specimens (strategically collected to cover the temporal nature of pregnancy) that allows for assessing maternal, placental, and fetal compartments; and improved access to high-quality and complete electronic medical records are critically important foundational elements needed to advance our capacity for risk prediction and causal inference studies. Other initiatives considered important for addressing the challenges above include:

- 1) Increasing the use of well-established prediction methods from other disciplines
- 2) Exploring newer sparsity methods with large numbers of variables

- 3) Improving the use and validity of vital statistics and hospitalization data
- 4) Enhancing clinical research environments to allow for the collection of data and biological specimens across the 24/7 clinical schedule

Breakout Group 2: Balancing Maternal and Fetal Risks and Timing of Delivery

Almost daily, obstetrical care providers have to evaluate the maternal and fetal risks of an intervention—including delivery—versus expectant management. This decision is complicated by the fact that the maternal risk or benefit is frequently in conflict with that of the baby.

Examples of decisions involving such a dilemma include those involving complications in the periviable period, such as route of delivery, tocolysis, and steroid administration for lung maturity. Gestational weight gain is another area where balancing maternal and fetal outcomes is a concern: the weight gain that is optimal for the mother may be detrimental to the fetus. So, too, is deciding in the intrapartum period between intervention for dystocia or fetal distress versus allowing labor to continue.

Breakout Group 2 concentrated on the area where this balancing act is most complex, namely, decisions involving timing of delivery. Conditions that frequently involve such decisions include fetal growth abnormalities, diabetes, hypertensive disorders, placental abnormalities, rupture of membranes, amniotic fluid abnormalities, multiple gestations, and repeat cesarean sections. While most of these cases typically fall into the “late preterm birth” category, they sometimes require decisions earlier in gestation. These conditions represent some of the most pressing problems in obstetrics today and should be viewed as opportunities to improve health care.

Many of the conditions listed above become evident as a result of current prenatal care practices, such as screening for aneuploidy, ultrasound imaging, and blood pressure measurement. Therefore, obvious opportunities for advancing scientific understanding would include evaluating current obstetrical practices and their effect on maternal and fetal outcomes, and designing rigorous trials to determine best approaches to managing these conditions, including optimal timing of delivery.

Because timing of delivery in these situations involves balancing maternal and fetal risks, more accurate methods to evaluate these risks are needed. These methods may involve discovery of novel biomarkers and development of condition-specific multivariate models of risk assessment.

In addition, consistent definitions of outcomes (maternal and fetal) are a prerequisite for conducting such trials. These may be definitive (death or major morbidity) or surrogate outcomes. While short-term outcomes are often a necessary first step, evaluation of long-term outcomes should be the ultimate goal. Decision analysis might help practitioners determine the appropriate balance between the two. These outcomes should also be meaningful and not just limited to the dire ones. It is time to include metabolic and cardiovascular consequences—for both mother and child—as well as the child’s school readiness and performance among the meaningful outcomes to evaluate in connection with obstetrical interventions.

Because decisions regarding the timing of delivery involve discussions between the health care provider and the patient and her family, the group felt that an opportunity to study the social context and determinants of these decisions exists. Comparative effectiveness research will play an important role in determining the ability to deploy specific interventions in the population.

Finally, because the placenta is frequently involved in these conditions, an opportunity exists to translate placental research, including basic science research, into actionable clinical markers. Tools to evaluate placental function and health non-invasively and repeatedly are needed. These tools may involve imaging (ultrasound, MR, or Doppler) or biochemical tests. Similarly, investigators should take advantage of the opportunity to develop longitudinal non-invasive monitoring of fetal physiological processes that are at risk for deterioration during expectant management, including functions of the brain, heart, and kidneys.

In order to address these opportunities, the group identified the following as priorities: using animal and in vitro models, linking available information from pregnancy to the neonatal and child periods, and using observational studies to define markers and pathways.

Ultimately, large, long-term cohort studies and appropriately designed trials will be needed. Tools to analyze complex systems and comparative effectiveness research will be indispensable.

Breakout Group 3: Preventing Cesarean Deliveries

In the United States, one in three infants is delivered by cesarean section; this translates to more than one million births annually. Over 90% of subsequent pregnancies among these mothers will be delivered by repeat cesarean, and women with multiple cesarean deliveries are at increased risk for complications such as placenta accreta, uterine rupture, adhesive disease, and difficult repeated surgeries, conditions that place both the mother and her future children at risk. Failure to progress in labor and concern for fetal status are the leading proximate causes of the first cesarean and of repeat cesarean delivery among those attempting a vaginal birth after cesarean section.

Survey results from the workshop participants indicated that few believe current techniques allow accurate and timely diagnosis of labor arrest (87% disagreed or strongly disagreed) or accurately identify those fetuses at risk for complications of hypoxia and acidosis (84% disagreed or strongly disagreed). The results also indicated that many participants think first cesarean deliveries increase the potential for long-term consequences to the health of the mother and her offspring (70% agreed or strongly agreed).

The group discussed many opportunities for addressing these concerns through research. Collaboration was a central theme. Members identified as priorities collaboration with industry, in the development of linked information systems to track mothers and their offspring long-term; biomedical and computational engineers, in the development of modern techniques for evaluation of labor progress and fetal status; and social science researchers, to better understand and address social and behavioral factors related to intrapartum management and cesarean delivery.

An improved understanding of the biology of parturition and how it relates to normal and abnormal labor can be accomplished with novel technologies that assess the mechanics (e.g., microprocessors and pressure transducers) and biology (e.g., translational proteomic analyses, reproductive hormonal milieu) of uterine function and labor. These clinical and biological markers can then be used to identify predictive markers for successful labor and improve the understanding of factors associated with abnormal labor outcomes.

Current intrapartum management relies heavily on traditional clinical tools (e.g., clinical pelvimetry, digital examination, tocodynamometry, and fetal heart rate monitoring). Objective metrics to evaluate labor progress and fetal status will allow health care practitioners to distinguish between women who should and should not undergo a first cesarean delivery for labor rest or for fetal indication. Modern technologies also should be developed to objectively measure components of labor progress, such as the strength of contractions, pelvic dimensions, and cervical compliance.

In addition, developing a definition of success when labor is induced—for example, the percentage of induced births that are delivered vaginally—and developing ways to predict outcomes when inducing labor will be welcome and important contributions. Given changes in clinical characteristics of the diverse American population, customized labor curves are needed to allow appropriate evaluation of labor progress. Validated techniques (e.g., electronic fetal heart rate monitoring, fetal pulse oximetry, and fetal EKG analysis, alone or in combination) are needed to accurately assess fetal status. These improved technologies will help prevent unneeded cesarean delivery and may lead to more timely indicated first cesareans before complications ensue.

The final priority area of investigation is the social, behavioral, and systems factors that impact labor management and cesarean delivery decision making by women and their health care providers. The impact of women's preferences, expectations, and external forces on their attitudes regarding intrapartum care and route of delivery, and of factors affecting physician interpretation and responses to measurements of fetal status and labor progress, need to be better understood. The influence of practice culture (economic, convenience, local norms, staffing) and factors external to clinical practice (medicolegal pressures, hospital policies) on intrapartum management and cesarean delivery rates also need to be elucidated. This work would be complemented by studies of labor interventions that aim to decrease the rate of primary cesarean delivery due to labor arrest or fetal distress, and to determine the optimal timing of delivery (induction vs. expectant management). Provider education tools (e.g., simulation) regarding fetal heart rate assessment and labor interventions, and feedback tools regarding care processes and practices leading to cesarean delivery should be studied to determine their impact on the rates of primary and repeat cesarean deliveries.

Breakout Group 4: Pregnancy and Future Health

Pregnancy offers a unique opportunity to study adaptive and maladaptive responses to physiologic changes. Understanding the underlying determinants of successful adaptation or the development of clinical manifestations of cardio-metabolic dysfunction would allow

implementation of interventions to improve pregnancy outcome. Such findings could also possibly help prevent or delay chronic disease, improving lifelong health for women.

In developing a conceptual framework for research, the challenges included the long time frame needed to obtain lifecourse information on women and their offspring, and the broad range of data on biology, exposure, and outcome required. This highlights the need for long-term (60+ years), intergenerational data. To achieve this in the next 10 years, we propose the use of existing pregnancy, birth, and youth cohorts. These cohorts will provide the components necessary to more fully understand the environmental exposures, physiologic changes, and molecular and genetic epidemiology related to long-term health and disease.

In addition, they will provide key information that will help characterize a woman's cardio-metabolic risk and exposures (including genetic variation) prior to conception. However, to make this information accessible, investigators will have to develop methods combining data across many cohort studies. Ultimately, these data would provide the basis for a prospective study with nested randomized controlled trials (RCTs) (Fig. 2 in the appendix).

This prospective study would allow investigators to collect data about environmental and behavioral exposures, concurrent with molecular phenotyping data. During the inter-pregnancy interval, women who developed a specific condition of interest in pregnancy (e.g., gestational diabetes mellitus, or GDM) would be randomized (nested RCT) into prevention/intervention and usual care groups. The efficacy of the intervention would initially be determined by the occurrence of complications in the subsequent pregnancy. All women enrolled in the initial cohort (regardless of inclusion in a randomized trial or subsequent pregnancy) as well as their children, would continue to be followed long-term regarding their health.

Use of alternative approaches, including short-lived animals, cell models, and computational models, to elucidate biologic mechanisms is also strongly encouraged. A reductionist approach to understanding the mechanisms, fully employing the armamentarium of the "omics" approach, is necessary in order to understand the intergenerational changes in a short period of time. Only when we understand the underlying mechanisms will we be able to develop interventions which have a basis for success.

Breakout Group 5: Prenatal Diagnosis

"Prenatal diagnosis" was broadly defined to include the detection of fetal aneuploidy, other congenital anomalies, and other abnormalities of fetal growth and development. Prenatal diagnosis of intrauterine growth restriction (IUGR) was assigned a high priority by both the breakout and overall groups because current standards of care result in only a 20% sensitivity of detection and a 70% false positive rate (Mattioli et al., 2010; Chauhan et al., 2006), which contrasts with the current 96% sensitivity and 5% false positive rate of detection of Down syndrome (Malone et al., 2005).

Prenatal diagnosis of an abnormality can and should be viewed as an opportunity to treat both the fetus and the pregnant woman during gestation. To date, fetal therapies have been predominantly surgically based; medical therapies and novel treatment approaches incorporating "omics" data

are warranted. Interventions that occur during fetal life should be designed to reduce the impact of chronic pediatric diseases and adult diseases that are fetal in origin without increasing the mother's risk.

A futuristic vision of prenatal diagnosis in 10 years might include early recognition that conception had occurred; bi-directional remote communication with the health care provider via smart phone applications; monitoring of critical environmental exposures early in the first trimester; and a first-trimester based screening strategy that incorporates biomarkers, DNA sequence data, fetal anatomy, and assessment of the placenta. Advanced algorithms built to consider all these data over time would then help investigators and health care providers classify each pregnancy along a continuum of risk and develop a personalized plan to manage each pregnancy. The majority (90%) of pregnant women would be low-risk and would not need the office-based monitoring utilized in today's obstetrical practices. The use of home-based monitoring would potentially save significant health care dollars. Resources would then be concentrated on the 10% of women at risk for developing complications of pregnancy.

Breakout Group 6: Placental Medicine and Syndromes

There are significant knowledge gaps in the field of placental biology and medicine, reflecting inadequate molecular and cellular definition of placental phenotypes and their association with fetoplacental disorders, maternal health complications, neonatal diseases, and subsequent predisposition to adult diseases.

Longitudinal investigations into normal placental development and function are urgently needed, including analysis of placental implantation, morphogenesis, differentiation, metabolism, maternal-fetal signaling and transport, and fetal immunological protection. Focused studies are necessary on the impact of assisted reproductive technologies, multi-fetal gestation, and the effect of gestational carriers (i.e., surrogacy) on placentation. Moreover, deciphering placental interaction with intrauterine, maternal, and external environments at early and late developmental stages is essential.

Modern investigative tools provide unprecedented opportunities for breakthroughs in this field. The use of functional genomics, integrated with other high-throughput "omic" tools (which we term "placenta on a chip"), enable improved molecular definition of placental biology and disease phenotype. These approaches should be bolstered by the use of novel animal models, including placental lineage-specific genetically altered mice, and efficient use of non-human primates. New macro- and micro-imaging modalities, and mathematical models of perfusion and metabolism, can serve to illuminate placental physiology and pathophysiology. Together, these tools may usher in new diagnostic and therapeutic approaches, including the use of bioengineering and human trophoblast progenitor cells in placental regenerative medicine.

Progress in the field will be accelerated by the formation of national and international research consortia and centers of excellence designed to establish diverse and comprehensive placental bio-repositories, including databases and biobanks of placental tissue, umbilical cord, amnion, chorion, and decidua from all gestational ages. Criteria and standardized protocols for data and specimen procurement should be defined by groups of experts that include biologists, clinicians,

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informaticians, and pathologists. They will assure that crucial information is captured and adjudicate responsible data access for the entire research community.

Breakout Group 7: Preterm Birth

Despite years of concern and scientific investigation, premature birth remains a principal cause of infant death, childhood disability, disparities in child health, and rising child health care costs. A new research and action initiative has the potential to generate major progress in preventing premature birth over the next decade. However, to reach this goal, business as usual will have to be replaced by a far more innovative and coherent research agenda.

Future research on this topic would ideally include a direct focus on developing preventive responses to known determinants; the development of intensive investigative agendas on joint candidate arenas of interdisciplinary integration; and the development of innovative mechanisms of research integration.

Among the most urgent objectives in prematurity research are the elimination of preventable iatrogenic premature births; research on improving risk assessment (including new biomarkers) and risk/benefit assessments for the major clinical profiles generating large numbers of iatrogenic premature births; and research on the enhanced targeting of extant interventions (including medications, such as anti-inflammatories or hormonal derivatives) to the relevant subsets of premature births.

This group also identified areas of joint investigation: the purposeful linkage of research in two or more areas that are both highly promising and likely to be highly interactive with each other. For example, the search for infectious etiologies and stress-related, neuroendocrine or immunologic pathways may prove more likely to produce actionable preventive strategies if greater interaction is facilitated. A selected set of pivotal, joint arenas of investigation could be identified for enhanced interaction and integration.

Any effective research agenda on premature birth will require new ways of facilitating intensely interdisciplinary research. Of special focus for research on premature birth is the linkage of extant datasets to allow the analysis of gene-environment interaction; the development of “multi-use” biologic specimen collection systems; exploration of complex systems analytic strategies; and the brokering of basic and social science interactions.

CONCLUSION

We believe that as the global disease burden shifts from acute to chronic disorders, research using pregnancy as a paradigm provides a unique opportunity to improve the long-term health of women and their children, transforming treatment to disease prevention.

In addition, compared with other areas of child health, pregnancy is understudied, and pregnancy research suffers from a scarcity of resources.

Taking advantage of the following key opportunities will help advance pregnancy research and improve the health of women and their offspring:

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- The use of emerging technologies and development of better methods to serially and non-invasively predict, screen, diagnose, and categorize antepartum and intrapartum complications.
- Performing clinical trials to determine the best management for common pregnancy conditions and for improving the future health of the mother.
- Leveraging research tools—such as birth cohorts and observational studies—that already exist, in addition to the development of evidence-based human research grounded on mechanistic laboratory models. Developing new tools for pregnancy research, including advanced animal models.
- Investigation of the biology of the placenta in order to understand embryonic development and feto-maternal crosstalk and, consequently, pregnancy health and disease. Integrated informatically-analyzed genomics and epigenomics data should be combined with other high-throughput, “omic” tools (“placenta on a chip”) to efficiently interrogate placental biology in the context of its unique fetal-maternal environment.
- Recognize pregnancy as a network of players at multiple levels, including genes, molecules, cells, tissues, organisms and the environments in which they live. Data about these harmonized, pregnancy-centric biological networks can define a “gestome,” which can be combined with medical and social information in order to fully understand gestational health.
- Appreciating the complex interactions of biology and social environment that affect pregnancy outcomes and embracing the transdisciplinary approach to advance progress in pregnancy-related research.

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Appendix: Figures 1 and 2

Figure 1. Timeline for events between conception and birth

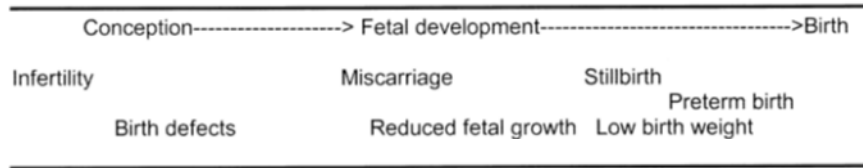


Figure 2. Model to examine the trans-generational effect of pregnancy on G1 and G2 generations over the entire lifespan

		G0 → G1 → G1 → G2 → G2 → G2	G0 G1 G2 G2 G2
Who	G0 = Pregnant Women	G1 = Children of G0	G2 = Grandchildren of G0
Age at entry	16 – 45	Birth	Birth
Age at end of 10y	26 – 55	10	
Age at end of 60y	76 – 105	60	15 – 46
Examples of data to collect across life of all generations	DNA	DNA	DNA
	Plasma & serum	Plasma & serum	Plasma & serum
	Behavior, e.g., diet, physical activity, smoking	Behavior, e.g., diet, physical activity, smoking	Behavior, e.g., diet, physical activity, smoking
	Cardiometabolic risk factors and events	Cardiometabolic risk factors and events	Cardiometabolic risk factors

Views expressed herein are the opinions of the authors and do not necessarily reflect those of the NICHD.

**NICHD Scientific Vision Workshop
on Pregnancy and Pregnancy Outcomes
February 22–23, 2011
Bethesda, MD**

Participant List

Special thanks to the workshop participants, who contributed to the ideas in this white paper:

Alfred Z. Abuhamad, M.D., FACOG
Eastern Virginia Medical School
Norfolk, VA

Richard H. Beigi, M.D., M.Sc.
University of Pittsburgh
Pittsburgh, PA

Diana W. Bianchi, M.D.
Tufts University
Boston, MA

Sean C. Blackwell, M.D.
University of Texas Health Science Center
at Houston
Houston, TX

Catalin Buhimschi, M.D.
Yale School of Medicine
New Haven, CT

Irina Buhimschi, M.D., M.M.S.
Yale School of Medicine
New Haven, CT

Brian M. Casey, M.D.
University of Texas Southwestern Medical
Center at Dallas
Dallas, TX

Karen Casey
Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Patrick Michael Catalano, M.D.
Case Western Reserve University
Cleveland, OH

Laura Caulfield, Ph.D.
Johns Hopkins Bloomberg School of Public
Health
Baltimore, MD

Francis Sessions Cole, M.D.
Washington University in St. Louis
St. Louis, MO

Deborah L. Conway, M.D.
University of Texas Health Science Center
San Antonio, TX

Deborah A. Driscoll, M.D.
University of Pennsylvania School of
Medicine
Philadelphia, PA

Francine H. Einstein, M.D.
Albert Einstein College of Medicine
Bronx, NY

William A. Grobman, M.D., M.B.A.
Northwestern University Feinberg School of
Medicine
Chicago, IL

Maureen Hack, M.D.
Case Western Reserve University
Cleveland, OH

Nazeeh Hanna, M.D.
State University of New York at Stony
Brook
Mineola, NY

Sylvie Hauguel-de Mouzon, Ph.D.
Case Western Reserve University
Cleveland, OH

Carol R. Hogue, Ph.D.
Emory University Rollins School of Public
Health
Atlanta, GA

Donna D. Johnson, M.D.
Medical University of South Carolina
Charleston, SC

K.S. Joseph, M.D.
University of British Columbia
Vancouver, Canada

Andrew Kasarskis, Ph.D.
Pacific Biosciences
Menlo Park, CA

Jay D. Kerecman, M.D., USAF
Uniformed Services University of the Health
Sciences
Bethesda, MD

Michael S. Kramer, M.D.
McGill University
Montreal, Canada

Robert H. Lane, M.D.
University of Utah School of Medicine
Salt Lake City, UT

Michele R. Lauria, M.D.
Dartmouth-Hitchcock Medical Center
Lebanon, NH

Debbie A. Lawlor, M.D.
University of Bristol
Bristol, United Kingdom

Ellice Lieberman, M.D., Dr.P.H.
Harvard School of Public Health/
Harvard Medical School
Boston, MA

Charles Lockwood, M.D.
Yale School of Medicine
New Haven, CT

Carole Mendelson, Ph.D.
University of Texas Southwestern Medical
Center at Dallas
Dallas, TX

Brian M. Mercer, M.D.
Case Western Reserve University School
of Medicine
Cleveland, OH

Kenneth J. Moise, Jr., M.D.
Baylor College of Medicine
Houston, TX

Leslie Myatt, Ph.D.
University of Texas Health Science Center
San Antonio, TX

Roger B. Newman, M.D.
Medical University of South Carolina
Charleston, SC

Anna Penn, M.D., Ph.D.
Stanford University School of Medicine
Palo Alto, CA

Robert Platt, Ph.D.
McGill University
Montreal, Canada

Aleksandar Rajkovic, M.D., Ph.D.
University of Pittsburgh
Pittsburgh, PA

Drucilla J. Roberts, M.D.
Massachusetts General Hospital
Boston, MA

Craig E. Rubens, M.D., Ph.D.

University of Washington
Seattle, WA

George R. Saade, M.D.

University of Texas Medical Branch
Galveston, Texas

Yoel Sadowsky, M.D.

University of Pittsburgh School of Medicine
Pittsburgh, PA

David A. Savitz, Ph.D.

Brown University
Providence, RI

Enrique Schisterman, Ph.D.

Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Jeanne Steinbronn Sheffield, M.D.

University of Texas Southwestern Medical
Center at Dallas
Dallas, TX

Baha M. Sibai, M.D.

University of Cincinnati College of
Medicine
Cincinnati, OH

Anna Maria Siega-Riz, Ph.D.

University of North Carolina, Chapel Hill
Chapel Hill, NC

Caroline Signore, M.D., M.P.H.

Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Robert M. Silver, M.D.

University of Utah School of Medicine
Salt Lake City, UT

Gordon C.S. Smith, M.D.

University of Cambridge
Cambridge, United Kingdom

Geeta K. Swamy, M.D.

Duke University Medical Center
Durham, NC

Elizabeth A. Thom, Ph.D.

George Washington University
Washington, DC

Steve Thornton, M.D.

Peninsula College of Medicine and
Dentistry
Exeter, United Kingdom

Alan Thevenet N. Tita, M.D., Ph.D.

University of Alabama at Birmingham
Birmingham, AL

Tyler VanderWeele, Ph.D.

Harvard School of Public Health
Boston, MA

Michael W. Varner, M.D.

University of Utah
Salt Lake City, UT

Martha M. Werler, Sc.D., M.P.H.

Boston University School of Public Health
Boston, MA

Allen J. Wilcox, M.D., Ph.D.

National Institute of Environmental Health
Sciences
National Institutes of Health
Research Triangle Park, NC

Michelle A. Williams, Sc.D.

University of Washington School of Public
Health
Seattle, WA

Paul Howard Wise, M.D.
Stanford University School of Medicine
Stanford, CA