A framework for strategic investments in research to reduce the global burden of preterm birth

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Preterm birth and stillbirth are among the greatest health burdens associated with pregnancy and childbirth. Fifteen million babies are born preterm each year, causing about 1 million deaths annually and lifelong problems for many survivors; 3 million stillbirths also occur annually. Worldwide, the number of women and children who die during pregnancy and childbirth exceeds the total number of births in the United States. New approaches could provide a greater understanding of prematurity, stillbirth, and maternal complications of pregnancy and childbirth. Integrated multidisciplinary investigations of the mother, fetus, and newborn in different contexts and populations could elucidate the biological pathways that result in adverse outcomes and how to prevent them. Descriptive research can determine the burden of disease, while more mechanistic discovery research could explore the physiology and pathophysiology of pregnancy and childbirth. Together, this research can lead to the development and delivery of new and much more effective interventions, even in low-resource settings. Recent surveys of researchers and funders reveal a striking lack of consensus regarding priority areas for research and the development of interventions. While researchers enumerate unanswered questions about pregnancy and childbirth, they lack consensus on priorities. Funders are equally uncertain about research and development projects that need to be undertaken, and many are hard-pressed to support research on the complex problems of pregnancy and childbirth given competing priorities. This lack of consensus provides an opportunity to engage with funders and researchers to recognize the importance of understanding healthy pregnancies and the consequences of adverse pregnancy outcomes. A strategic alliance of funders, researchers, nongovernmental organizations, the private sector, and others could organize a set of grand challenges centered on pregnancy and childbirth that could yield a substantial improvement in reproductive health.

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oday, mothers and their children around the world pay an immense toll in terms of mortality and morbidity due to a lack of knowledge about pregnancy, childbirth, and early life. Fifteen million babies are born prematurely each year, causing about 1 million of the >3 million neonatal deaths that occur annually. Prematurity is now the second leading cause of death in children <5 years of age and the leading cause of death in the first month of life. Three million stillbirths occur globally each year, and more than a quarter million women die from complications during pregnancy and childbirth. The health effects of prematurity extend far beyond birth. Prematurity increases the risk for hypertension, mental health disorders, chronic respiratory disease, and neurologic and learning disabilities.

Despite the enormity of these problems, research on pregnancy is not well coordinated and is far too limited in scope, and funding is not scaled to the enormity of the burden in the developed and developing world. But preterm births create large health care costs—estimated in 2005 in the United States as $26 billion annually in short-term health care costs alone. Likewise there is a disparity in resources allocated to research on care of the preterm infant rather than on research that will lead to prevention strategies. A balanced research agenda that emphasizes prevention as well as care of the woman in preterm labor and the preterm infant is paramount to decrease the impact of morbidity and mortality caused by preterm birth around the globe. A variety of factors contribute to the relative neglect of research on pregnancy, childbirth, and early life. Pregnancy is extremely complicated scientifically, yet nonscientists view it as a straightforward, normal life event. Often, political pressures bring focus on other diseases. Historically, research on women’s health issues has been slighted, and in many parts of the world women still lack basic health care and fundamental human rights. Thus, pregnancy remains one of the least explored aspects of human biology, creating a tremendous opportunity. Long-term funding commitments for research could advance discovery science and the development of interventions targeted at pregnancy and early life and impact maternal and newborn health around the world.

To address these opportunities and funding challenges, The Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) gathered and synthesized information on the health of women and their children from conception to age 2...
years. This paper presents the analyses of information from 3 sources: a technical team of experts convened by GAPPS to review research in this area and identify gaps that need to be filled; perspectives and insights of prominent scientists who are familiar with but not directly involved in research on pregnancy, childbirth, and early life; and representatives of organizations that fund large-scale research and intervention efforts in health-related areas.

The intent was to facilitate the development of a scientific and strategic framework showcasing the critical need for strategic research related to the health of women and their infants. By identifying common ground and possibilities for collaboration between key stakeholders, it provides a framework for engagement of a broad alliance of funders, researchers, and advocates to raise the profile of research on pregnancy, childbirth, and early life.

A scientific framework

The GAPPS technical team of 13 prominent researchers from multiple disciplines in the developed and developing world worked to help outline a research agenda related to pregnancy, childbirth, and early life (listed in acknowledgments). Their analysis began with the assumption that health problems that occur during pregnancy, childbirth, and early life are complex syndromes with multiple causes and outcomes, occurring on a continuum that begins at conception. Understanding the determinants of a healthy pregnancy and the mechanisms responsible for adverse outcomes is one of the most difficult, as well as one of the most important, questions in biomedical research today. It requires an interdisciplinary approach. Different biological pathways are involved in the adverse outcomes of pregnancy, and these can be characterized at different biological levels, from the genome to the exposome (the combined effects of environmental influences). All of these causes and mechanisms will need to be studied through integrated investigations of the mother, fetus, and newborn.

Healthy pregnancies can have different characteristics in different contexts and among different population groups. Research in different settings and with different populations will produce results that are more widely applicable than research that is limited to high-resource countries.

Closing the knowledge and solution gaps

The technical team observed that current research funding is fragmented and uncoordinated, lacking central leadership. Funders do not understand where the field is going; this undercuts any systematic approach to prioritizing research investments. Research focuses excessively on short-term outcomes rather than long-term prevention of adverse health outcomes. Further, there has been a failure to fund implementation research, and existing effective interventions have not been analyzed in a way that they can be scaled up and implemented elsewhere.

Understanding pregnancy will require both descriptive research to characterize the attributes of healthy pregnancies and adverse outcomes and discovery research to probe the determinants and consequences of those outcomes (Table 1). Descriptive research is needed to define pregnancy outcomes and correlate outcomes with fetal, infant, and early life development across a range of contexts and settings. This should include data from prospective longitudinal studies of mothers to determine the burden of childhood and adult disease attributable to adverse pregnancy outcomes. It also requires standardized definitions and classification schemes, including risk factors, phenotypic definitions, disease classifications, and outcomes.8

Discovery research is needed to explore the physiology and pathophysiology of fetal, neonatal, infant, and early childhood development. State-of-the-art technologies can elucidate the many different biological pathways involved in pregnancy and early life. High-throughput systems biology can help unravel the complex biological networks at the heart of pregnancy and early life. Basic research into genomics, epigenetics, pathophysiology, and epidemiology will continue to generate new therapeutics, diagnostics, preventive measures, services, and education. Particularly promising is the potential development of validated biomarkers of healthy pregnancies and adverse outcomes in the short and long term for the mother and child.

Few interventions exist today to reduce preterm birth. Even if all the current interventions were universally applied, we estimate that the preterm birthrate would drop by <20%. And, many of those interventions would be impossible to implement fully due to cultural and resource constraints. Research leading to new, low-cost, high-impact interventions could achieve large health gains.

Descriptive and discovery science can lead to the development and delivery of effective interventions that may include nutritional modifications, changes in environmental exposures, improved care during pregnancy, or identification and control of infection. Economic modeling of the cost and burden of disease and the costs of interventions can help generate support for additional research or scaled-up interventions. Technology transfer and adaptation are needed to enable the appropriate
use of technologies in low-resource settings and between countries. Predictive algorithms using easy-to-assess risk factors need to be developed for all settings that are able to robustly predict later risk to mother and child based on pregnancy outcomes and other biomarkers.

As with efforts to close the knowledge gap, closing the solutions gap requires an interdisciplinary approach. New multidisciplinary structures will be needed to link research with the development of interventions in a productive interchange.

Coordinating research and implementing interventions
Closing the knowledge and solution gaps requires a coordinated research and funding strategy. A system of integrated global multidisciplinary research centers could provide sustainable intellectual leadership, promote increased collaboration, and support longitudinal mapping studies of pregnancy—tracking what might be called the “gestome.” In particular, detailed longitudinal follow-up of children is needed to determine the burden of childhood and adult disease that is attributable to adverse pregnancy outcomes. Strengthening the research infrastructure in low- and middle-income countries (LMICs) is needed to facilitate collection of essential longitudinal data on mothers and their children. A system of global biorepositories in LMICs as well as in high-income countries could support research and development through, for example, the international development, harmonization, and validation of biomarkers. This work requires a combination of low-technology methods and high-throughput systems biology to assess biomarkers and health outcomes along with bioinformatic tools to disseminate capabilities and information widely. Biobank materials should include, with appropriate demographic data, specimens from mothers, newborns, and fathers. Tissue collection, separation, and storage techniques need to be improved. Future samples will need to be collected, processed, and stored under standardized protocols. Pairing these samples with rich phenotypic data will expand research opportunities.

The interdisciplinary research that is needed calls for professional development to build cross-disciplinary expertise and promote collaboration within and between countries and between discovery, development, and implementation research. Opportunities exist for translational research and development in high-burden settings to lead to scalable interventions. Descriptive and discovery science will facilitate development of and delivery of interventions. Similarly, implementation and delivery of effective interventions will stimulate discovery science and may lead to further refinement of prevention strategies in a positive feedback fashion (Figure).

While descriptive and discovery research continues, implementation research needs to identify existing appropriate interventions, determine whether they are being implemented, and understand the barriers to implementation. It should conduct economic modeling to demonstrate the costs and benefits of early vs late interventions. It should monitor the efficacy of new interventions and probe social, cultural, and political attitudes toward ad-
verse pregnancy outcomes, including attitudes associated with prematurity and stillbirth.

In addition to the work by the technical team, interviews with 7 prominent scientific thought leaders were conducted to provide additional insights into research on pregnancy, childbirth, and early life. None of the scientific thought leaders had worked directly on stillbirth or prematurity, but each was familiar with the field and had extensive experience organizing and conducting research in related fields. Two were based in the United States, 5 in other countries, and together they represented multiple research disciplines, including the social sciences. They were told that their names would not be used in analyses of their perspectives.

The interviews with the scientific thought leaders revealed a remarkable diversity of perspectives. The interviewees mentioned many valuable areas of research, from basic biological mechanisms to access to pregnancy services. The range of needed research identified was daunting, indicating the tremendous promise of increased investments in this area. The scientific thought leaders identified several reasons why research on pregnancy is underfunded compared with other areas, including a lack of political pressure, the undervaluing of women and reproductive health issues, and the biological complexity of pregnancy and childbirth. The political pressure for action in this area is diffuse, unlike with AIDS or breast cancer. Pregnancy and childbirth are often perceived as normal physiological events, and women have not traditionally been seen as a group that needs to be studied differently from the overall population. In addition, the solutions to prematurity and stillbirth have been seen as more nutritional or environmental and less pharmacological, reducing the economic incentive for private sector research and development. Social and cultural factors were also recognized as important determinants to pregnancy outcomes. Health care delivery and the training of service providers could have a major impact on maternal health. Simplified interventions are needed that LMICs can both afford and implement without expensive infrastructure. These were identified as current challenges. However, the situation is changing as awareness of the connection between fetal development and adult health increases. The new United Nations Global Women’s and Children’s Health strategy provides one opportunity to raise visibility.

To attract new investigators to pregnancy-related research, the scientific community needs to be made aware of the importance and potential of this field. A shift in emphasis is needed from poor outcomes affecting a small number of people to the fact that good outcomes benefit everyone. The scientific thought leaders thought this could be achieved through convening a panel of experts to identify the critical issues, review articles for the scientific community highlighting research achievements and potential, and funding opportunities that tie to adult diseases. In LMICs, links between biomedical research and the social aspects of pregnancy and childbirth could attract researchers and research funding. A grand challenge approach could move the field forward quickly. A panel of experts could identify critical issues and help generate a call for proposals. Multidisciplinary research groups could include not just biologists but nutritionists, public health researchers, and social scientists. The involvement of the Bill and Melinda Gates Foundation as both convener and funder could persuade key international players to participate.

| TABLE 2 |
| Toward making every pregnancy a healthy pregnancy |

- Emphasize that healthy outcomes in pregnancy benefit everyone, directly and indirectly
- Raise awareness of personal and public burden of prematurity, stillbirth, and other pregnancy and early life problems
- Establish strategic alliance of funders, researchers, and other stakeholders in areas of pregnancy, childbirth, and early life
- Identify commonalities among funding organizations to develop coordinated research and intervention agenda
- Identify and promote research opportunities in areas of pregnancy, childbirth, and early life that can attract investigators
- Engage new investigators from multiple disciplines
- Utilize descriptive sciences and economic modeling to establish true costs and burdens of disease and assess impact of costs of current or future interventions
- Establish collaborations and promote research within high-burden, low-resource countries


A funding perspective

Interviews were also conducted with 18 representatives of funding organizations—including government agencies, global foundations, and other financial partners—to gain a deeper understanding of the current perspectives, attitudes, and commitments of funders toward research on pregnancy, childbirth, and early life. The interviews sought to explore how healthy pregnancy ties in with broader development challenges and goals. The interviews also explored funders’ impressions of potential messages designed to increase funding on research from conception to age 2 years. The interviewees were told that their names would not be used in analyses of their perspectives.

There was a lack of a strong consensus regarding priority areas for research and the development of interventions. Although the interviewees generally saw research on pregnancy as underfunded, they identified different challenges in moving the field forward. In some cases, funders said that their investments in this area are limited because of the lack of clear research priorities. This lack of consensus represents a major opportunity to educate funders about the problem and draw on their disparate understandings to forge a more cohesive research agenda.

Levels of understanding and interest among potential funders

Funders exhibited a range of understanding of the issues, providing an
opportunity to engage with those who recognize the need and to educate others about the importance of understanding healthy pregnancy and the consequences of adverse pregnancy outcomes. Funders tended to disagree with the statement that most premature births could be prevented by scaling up current interventions, especially in the developed world. They also noted that not enough is known to predict which infants will develop chronic disease as a consequence of prematurity.

Funders also expressed varying degrees of interest in the topic. For some it is their highest priority, while others assigned it a lower priority in their research portfolio. Some funders observed that it is difficult to keep this research a high priority, given the challenges of progress with such a long-term and complex problem.

Funders also focused on different aspects of a healthy pregnancy. Some emphasized maternal nutrition and prenatal care. Others tied a woman’s socioeconomic status to the likelihood of her achieving a healthy pregnancy. Others hypothesized the existence of genetic variants that direct essential biochemical and physiological pathways. The availability of family planning and having control over childbearing were key priorities of some funders. Some funders had strong opinions about the establishment of global biobanks of specimens from mothers, newborns, and fathers. Many saw value in biobanks but were concerned that biobanks do not do enough to link specimens to the phenotypes and demography of patients.

Despite these differences, most funders agreed that defining a normal or healthy pregnancy needs to be the first step in ensuring a healthy pregnancy for all women. They noted that understanding of a normal pregnancy is limited and that more needs to be learned about the link between fetal and neonatal development and the occurrence of chronic disease later in life.

Another key interest area is outcome disparities across different groups. Many organizations are investigating these disparities in the context of broader health care concerns, providing an opportunity to coordinate this research with more narrowly focused investigations of disparities in pregnancy outcomes.

The organization of research
Funders had somewhat differing opinions regarding coordination of funding and a funding review process. Some saw coordination as very important, while others thought that it is less necessary and hard to accomplish. Coordination of funding efforts was seen as a challenge due to the diversity and number of organizations that would need to be engaged. Disparity in funding processes was also noted. In this research area, the assumption has been to fund program areas and organizations, but the interviewees also emphasized the need to engage scientists, and especially young scientists, on an individual level. Some of the funders believed that their priorities and review processes provided an adequate framework with which to identify investigators and fund them. Others found that it was difficult for their organizations to sort out what research to fund in this area. In general, funders need to believe that the problem is solvable and that their efforts are making a difference. Measures of return on investment may vary, but the interviewees agreed on the importance of being able to show results.

Several interviewees observed that the Bill and Melinda Gates Foundation has an unparalleled ability to persuade, convene, and organize important players, both nationally and internationally. In particular, they pointed to the potential for the foundation to move the concept of coordinated funding forward.

Recommendations
From the 3 sources of information described in this document, we have compiled a set of recommendations that could greatly improve the visibility of research on pregnancy, childbirth, and early life and mobilize funders to increase investments leading to the discovery, development, and delivery of low-cost and high-impact interventions (Table 2). These recommendations begin with the premise that healthy pregnancy outcomes benefit everyone. Reducing the burden of preterm birth and other adverse outcomes of pregnancy will require an alliance of funders, researchers, and key stakeholders in the areas of pregnancy, childbirth, and early life. To achieve this, it will be necessary to advocate raising awareness of the magnitude of prematurity, stillbirth, and childhood problems with both the public and the policymakers. Economic modeling of the true costs of prematurity and better epidemiologic science of the burden of prematurity will be critical in raising awareness. Common ground among funding organizations should be sought to develop a coordinated research and funding strategy and to attract new funding sources. After establishing an alliance for research funding, we can then identify and promote the many exciting research opportunities in pregnancy and childbirth that can attract investigators from multiple scientific disciplines. Finally, coordination of pregnancy-specific biobanks and harmonization of data collections will allow research in a context- and population-specific manner. Infrastructure must be developed and collaborative research encouraged within LMICs where the burden of disease is greatest. Finally, investigators and funders must find common ground to make every pregnancy a healthy pregnancy.

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REFERENCES


