Neurodevelopment: The Impact of Nutrition and Inflammation During Preconception and Pregnancy in Low-Resource Settings

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abstract

The rapid pace of fetal development by far exceeds any other stage of the life span, and thus, environmental influences can profoundly alter the developmental course. Stress during the prenatal period, including malnutrition and inflammation, impact maternal and fetal neurodevelopment with long-term consequences for physical and mental health of both the mother and her child. One primary consequence of maternal malnutrition, inflammation, and other sources of prenatal stress is a poor birth outcome, such as prematurity or growth restriction. These phenotypes are often used as indications of prenatal adversity. In fact, the original evidence supporting the fetal programming hypothesis came from studies documenting an association between birth phenotype and the development of subsequent physical and mental health problems. Fetal growth restriction in both term and preterm infants is associated with neonatal morbidities and a wide variety of behavioral and psychological diagnoses in childhood and adolescence, including attention-deficit/hyperactivity disorder, anxiety, depression, internalizing and thought problems, poor social skills, and autism spectrum disorder. Improving maternal–child health requires interventions that begin before pregnancy and continue throughout gestation and into the postpartum period. Such interventions might include supporting pregnancy intention, maternal nutrition, health/medical care, mental health, and providing social support. This article discusses the impact of maternal nutrition and inflammation during preconception and pregnancy among women living in low-resource settings, with an emphasis on key knowledge gaps that need to be addressed to guide program and policy decisions at local, regional and global levels.

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Healthy outcomes for both mothers and infants will require an emphasis on: preconception health; supporting pregnancy intention and avoidance of unintended pregnancies; the provision of comprehensive care and support during the prenatal, intrapartum, and postpartum periods; a continuation of this cycle with intended subsequent pregnancies; and optimal pregnancy spacing. Maternal stressors, including threats to psychological or physical viability, such as malnutrition and inflammation, are critical aspects of the preconception and prenatal environment that can have enduring consequences for fetal neurodevelopment. There are specific biological processes, including activation of the sympathetic nervous system, and the hypothalamic–pituitary–adrenocortical axis, that respond to these stressors. These biological processes orchestrate integrated responses that have evolved to increase survival in the immediate face of threat.[1] During pregnancy, these stress response systems are an important mechanism by which information about the external environment is communicated to the fetus. For example, in a high-stress environment, fetal growth may be restricted to preserve resources and increase chances of survival. The fetus and the fetal brain are "under construction" and signals received in utero influence the progression of fetal development. These early stress signals influence the timing of delivery, can contribute to preterm birth, and exert lasting influences on the brain and behavior throughout the life span.

KEY FETAL DEVELOPMENTAL CONSIDERATIONS DURING PREGNANCY

The transformation from a single-celled zygote to a human newborn is a dramatic and dynamic process. During gestation, the remarkable rate of development, particularly in the brain, is unmatched at any stage of the life span. Tissues develop in a specific sequence from conception to maturity, making different organs responsive to environmental influences at different times. The rapid pace of human brain development renders it susceptible to a variety of stimuli or insults at critical or sensitive periods of development with potentially lasting or lifelong effects, known as programming.[2,3] A critical period refers to a time in development when the presence or absence of a stimulus or insult results in irreversible change (eg, binocular vision), whereas a sensitive period refers to a time of heightened sensitivity to stimuli or insults followed by an extended period of ongoing responsiveness, but to a lesser degree (eg, language development).[4,5] Thus, the timing of the stimulus during development coupled with the timetable for organogenesis determines the nature of a programmed effect. Prenatal adversity often is associated with a restriction of fetal growth, with compensations in other organ systems in an attempt to protect the brain. For example, prenatal adversity may decrease fetal blood supply, resulting in shunting of blood from peripheral organs to the central nervous system (CNS). However, only partial protection is typically achieved, which may lead to long-lasting consequences for the developing brain.

The protracted period of human brain development renders it susceptible to adversity over a long period of time, extending into adulthood. The prenatal period represents a time of extremely rapid change in brain development.[6–9] During gestation, neurogenesis can occur at an astonishing rate of over 100 000 new cells per minute.[7,10] These rapid neurologic advances render the fetus susceptible to various influences with life-long implications. Human neurogenesis initiates on embryonic day 42 and is complete by midgestation.[11] Around the eighth gestational week, neuronal migration begins. By gestational week 20, axons form synapses with the cortical plate, and by gestational week 24, cortical circuits are organized.[12,13] By gestational week 28, the human brain contains billions of neurons, 40% more than in adulthood.[8,13,14] These new cells begin to communicate and, during the third trimester, the rate of synapse formation accelerates to a rate of 40 000 synapses per minute.[7] During the third trimester, the fetal brain is forming secondary and tertiary gyri and exhibiting neuronal differentiation, dendritic arborization, axonal elongation, synapse formation and collateralization, and myelination.[9,15] The fetal period is therefore a time of enormous neurologic change and, thus, experiences during this period can dramatically influence development.

In this article, we will discuss the influence of maternal individual and environmental risk factors, with a special emphasis on nutrition and inflammation, on fetal neurodevelopment in low-resource settings (LRS) (see Fig 1). The outcomes and consequences of these factors for the fetus, who becomes the neonate and then the infant, toddler, child, adolescent and, ultimately, an adult, and the impact of these factors on brain development will be presented.

THE IMPACT OF PRECONCEPTION AND PRENATAL MATERNAL NUTRITION ON FETAL NEURODEVELOPMENT

Maternal undernutrition is common in some settings, such as South Asia, where >10% of women have a BMI <18.[16] This undernutrition is associated with high rates of intrauterine growth restriction (IUGR), low birth weight

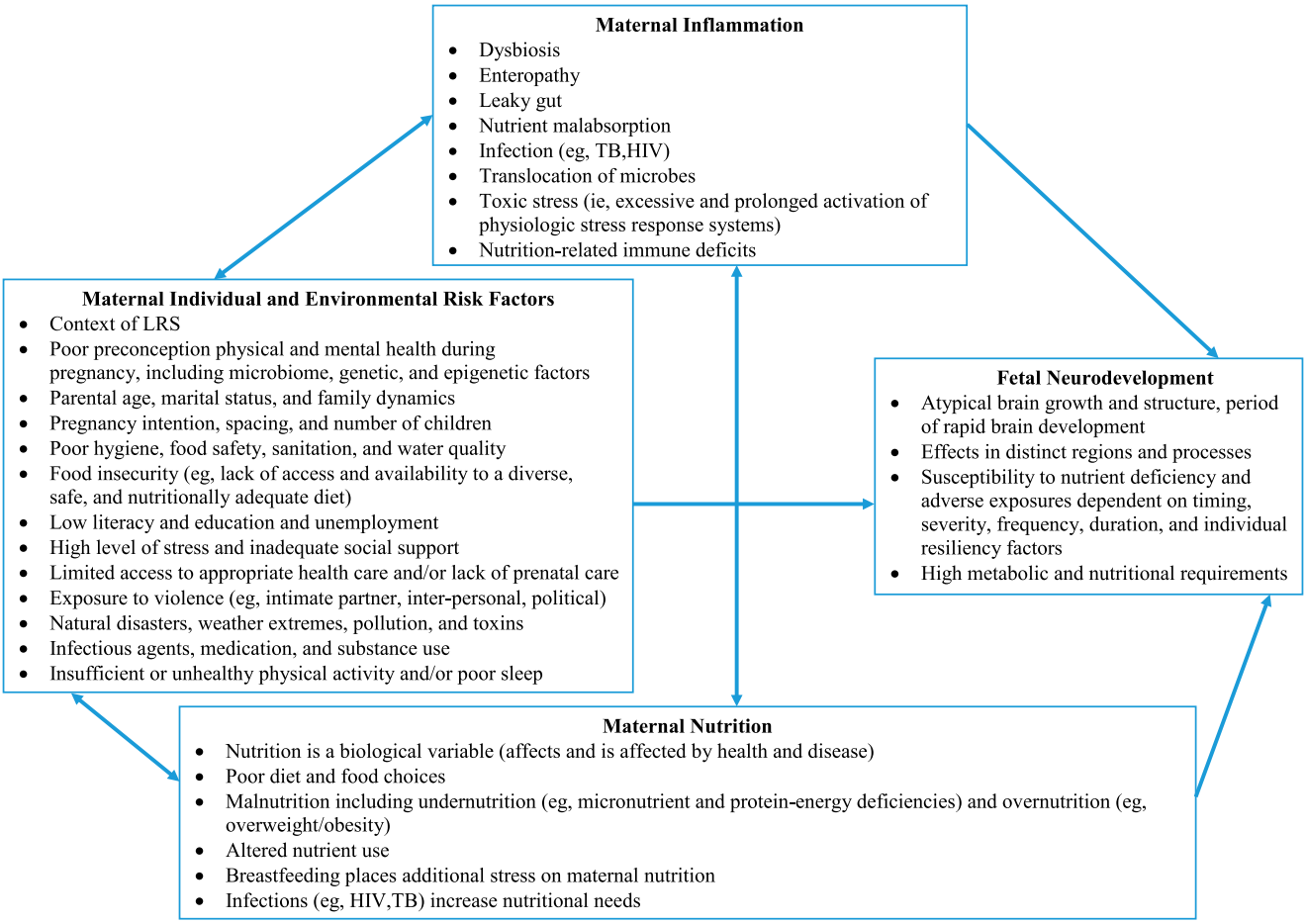

FIGURE 1
Influence of maternal individual and environmental risk factors, with special emphasis on inflammation and nutrition, on fetal neurodevelopment in LRS.

(LBW), and infants born small for gestational age. LBW and being small for gestational age account disproportionately for growth faltering, morbidity, and unrealized developmental potential. A low preconception BMI is a risk factor for poor birth outcomes.[17] Taking in adequate calories is not sufficient to optimize nutrition for the fetus, because dietary quality is of critical importance as specific nutrients are required during sensitive or critical periods of development. Infants born to malnourished women, especially those who experienced IUGR, are likely to have low tissue concentrations of critical nutrients at birth, essentially starting postnatal life with deficits.[16,18–21] Suboptimal maternal nutritional status during pregnancy, together with the potential risk for inadequate postnatal intake of those micronutrients for which maternal diet and status impacts the concentrations in breastmilk, likely compounds the risk for deficiencies in the offspring.

Associations between several micronutrient deficiencies and neurodevelopmental outcomes have been identified. First, folate is perhaps the best known nutrient that, when deficient, is associated with neural tube defects.[21] Second, choline is being recognized as important for the development of the neural tube.[22] Third, vitamin B_{12} contributes to DNA methylation and epinephrine synthesis, along with methionine synthesis.[21,23] Fourth, zinc is important for neuron formation, migration, and synapse generation,[24] and, if given as a supplement, can reduce the risk of preterm birth.[25] Fifth, tryptophan is an essential amino acid needed for the formation of neurotransmitters.[26] Sixth, Ω-3 fatty acids are necessary for the development of neural cell membranes.[27] Seventh, maternal iodine deficiency can disrupt fetal neurogenesis, neuronal migration, synaptogenesis, and myelination[28–30] and has the potential for ongoing postnatal effects due to low iodine levels in breast milk.[30]

Furthermore, iron deficiency is the most common nutrient deficiency globally. Iron is necessary for myelination and the development of the frontal cortex and basal ganglia.[31] Iron deficiency has been found to adversely impact cognitive, motor, socioemotional,

and behavioral development.[32–34] Given the benefits to most newborns and concordant with other professional organizations, the American College of Obstetricians and Gynecologists, effective January 2017, recommends a delay in umbilical cord clamping in vigorous term and preterm infants for at least 30–60 seconds after birth.[35] The ability to provide delayed umbilical cord clamping may vary among institutions and settings; decisions in those circumstances are best made by the team caring for the mother–infant dyad. In Latin America, delayed umbilical cord clamping has been found to be significantly associated with increased infant ferritin at 3 months of age and improved iron status at 6 months of age as measured by ferritin, mean corpuscular volume, the transferrin receptor to ferritin ratio, estimated total body iron, and storage iron.[36–38] In summary, only a few of the important nutrients required for healthy fetal neurodevelopment have been highlighted, which underscores the importance of a diet rich in diversity.

Moreover, the interconnectedness of preconception and prenatal maternal malnutrition, early infant diet, growth, and development is illustrated in a series of descriptive nutritional studies undertaken in 99 undernourished pregnant women and their infants in Sidama, Southern Ethiopia.[39–43] Thirty percent of the women were stunted, and the mean BMI in the third trimester of pregnancy was 21.7 kg/m^2; in addition, ~90% of energy was from cereal grain and enset (a banana-like fruit), and the prevalence of inadequate protein and zinc intake was 100% (although the prevalence was <10% for low iron intake).[39] Pregnant women's scores on tests of cognitive function were significantly associated with plasma zinc concentrations as well as maternal age and education.[42] Their offspring had high rates of poor linear and ponderal growth status,[43] and delays in motor developmental milestones were more frequent in stunted infants compared with their nonstunted counterparts.[44] The findings in this series of reports from a single setting not only illustrate the intergenerational perpetuation of malnutrition and its effects in that particular context, but also represent a scenario that is common to impoverished environments with poor hygiene and sanitation and limited access to high-quality health care in addition to malnutrition.[16,45]

It is important to note that malnutrition includes not only undernutrition, but also overnutrition (eg, overweight/obesity), which might consist of an excess of calories and an overweight status but with micronutrient deficiencies due to the consumption of foods of poor nutritional quality. Therefore, malnutrition refers to poor nutritional quality, including micronutrient deficiencies in both over- and undernutrition. Maternal obesity, a critically important public health challenge, is associated with adverse outcomes for both mothers and infants. In a recent review,[46] maternal obesity during pregnancy was associated with gestational diabetes, preeclampsia, gestational hypertension, depression, instrumental and cesarean birth, surgical site infection, greater risk of preterm birth, large-for-gestational-age infants, fetal defects, congenital anomalies, and perinatal death. Additionally, obesity is an inflammatory process and may exert influences on neurodevelopment through the effects of inflammation as well.[47]

THE IMPACT OF MATERNAL INFLAMMATION ON FETAL NEURODEVELOPMENT

Infections prevalent in low- and middle-income countries (LMIC), such as tuberculosis (TB), HIV, respiratory illnesses, malaria, and diarrheal disease, may be even more common in the pregnant woman, particularly in LRS. These infections are likely to alter the environment of the fetus through maternal fever, dehydration, stress, nutritional compromise, and other related symptoms.

The fetus in the intrauterine environment may be impacted by the full spectrum of infectious agents, with concomitant exposure to the resulting inflammatory cytokines. The risk for infection in the fetus and neonate, particularly premature neonates, is significant because they do not have mature physical or immunologic defenses. Chorioamnionitis, inflammation of the maternal or fetal placenta, ranges in severity from mild to severe and is recognized as a major cause of preterm delivery[15,16,48,49] The rate of chorioamnionitis is inversely related to gestational age, with an 80% incidence in infants born at 23 weeks.[50] An infant born in an LRS is at risk for both the impact of common maternal infections and exposures in the physical or social environment, including those related to local traditional or cultural practices. For example, the umbilical cord may be cut with nonsterilized instruments or, in some regions, the cut umbilical cord is coated with mud, which leaves the neonate at risk for tetanus and other infectious agents.

Viral infections of the fetus frequently involve the CNS and cause significant morbidity and mortality. Cytomegalovirus (CMV) is currently the leading cause of congenital infections worldwide, with an estimated annual prevalence of 0.4% to 0.7% in the United States and 1% to 5% in LMICs.[51,52] Infection occurs through mucosal contact with infected body fluids, persists for a lifetime, is often latent and then later reactivated, and is usually asymptomatic.[51] HIV coinfection can lead to progressive

immune impairment and higher risk for congenital infection.[52] CMV infection can be fatal for the fetus, but more commonly results in neurodevelopmental morbidity, including cognitive deficits and visual impairment.[51] Sensorineural hearing loss occurs in ~35% of infants with symptomatic infection and can occur with asymptomatic infection as well, with CMV being the most common nongenetic cause of permanent hearing loss.[51,52] Although the majority of neonates with CMV are asymptomatic at birth, they remain at high risk for developing significant sensorineural hearing loss, placing a significant burden on the family. Currently, treatment of infected neonates with antiviral agents has shown limited benefit. The development of vaccines to be tested in clinical trials to prevent primary or secondary maternal infection during pregnancy, eradicate infection in the developing fetus, and potentially decrease health care costs is indicated.[53,54] CMV is one of a group of pathogens associated with adverse outcomes, which may be acquired in utero or through the birth process, commonly referred to as the TORCH organisms: toxoplasmosis, other (syphilis), rubella, CMV, and herpes simplex.

In November 2015, the Brazilian Ministry of Health reported an unprecedented increase in the number of cases of neonatal microcephaly.[55] This report was followed by an Epidemiologic Alert by the Pan American Health Organization in December 2015 notifying member states of an increase in congenital anomalies, Guillain-Barré syndrome, and other neurologic and autoimmune syndromes in areas where Zika virus (ZIKV) was circulating.[56] A Public Health Emergency of International Concern statement by the World Health Organization followed in February 2016.[57]

Although there is increasing evidence of a causal link between maternal ZIKV infection, fetal microcephaly, intracranial calcifications, and other CNS and ocular abnormalities, the long-term impact of this pathogen on neurodevelopmental outcomes in affected infants is yet to be fully understood.[58–60]

Numerous studies have investigated the relationship between maternal infections and neonatal and child outcomes. Severe infections are associated with increased proinflammatory markers, including IL-6, IL-1, and tumor necrosis factor α.[61] Proinflammatory cytokines damage oligodendrocytes and their progenitors during a critical period of brain development, with resultant impairment of myelination in the brain. Both perinatal inflammation and infection contribute to the pathogenesis of this brain injury.[62–65] The preterm infant is particularly vulnerable to white matter injury, including cystic periventricular leukomalacia and noncystic multifocal white matter injury. White matter injury is associated with adverse neurodevelopmental outcomes, particularly cerebral palsy. Chorioamnionitis among preterm infants is additionally associated with impairments in gray matter development.[66] Gastrointestinal morbidities, including necrotizing enterocolitis and spontaneous intestinal perforation, are also associated with poor outcomes, including increased rates of cerebral palsy, significant developmental delay, feeding challenges, and failure to thrive.[67–69] Breast milk is an important, cost-effective intervention to decrease the risk of sepsis and necrotyzing enterocolitis.[70,71] Similar adverse outcomes have been reported with the occurrence of serious enteric illnesses, such as cryptosporidiosis, in LRS.[72]

THE IMPACT OF THE INTERACTION OF MATERNAL NUTRITION, INFLAMMATION, AND OTHER INFLUENCING FACTORS ON FETAL NEURODEVELOPMENT

There is a complex relationship between nutrition and inflammation in pregnant women. The mother needs to stay well-nourished for her own health while the fetus depends on the nutritional status of the mother for energy as well as for the specific nutrients that contribute to the structure, biochemistry, physiology, and function of the brain. Although weight and BMI are important, they are not sufficient to fully capture nutritional status. The quality of the dietary intake is also important, and the availability of food, as measured by a food insecurity survey, is critical for determining access to appropriate nutrition. A body of evidence is emerging that explores the link between diet and chronic inflammation. Consequently, investigators have developed a dietary inflammatory index, which can be used as a measure of inflammation, because some foods may be considered more inflammatory than others.[73] Factors identified in the nutritional assessment may contribute to inflammation, and, conversely, inflammation also has an impact on nutritional status. Although undernutrition or wasting is not necessarily an inflammatory process, its etiology may well be an inflammatory process, such as infection. HIV or TB infection increases metabolic demands and is likely to be associated with significant weight loss, even if treated.[74] Finally, obesity is considered an inflammatory process and is increasingly common in both high- and low-resource settings.[47]

As depicted in Fig 1, the environment of the pregnant woman also serves as the environment for the fetus. Some common factors that influence

TABLE 1 Recommendations for Research Initiatives To Address Knowledge Gaps

Problem or Question	Studies Needed
1.Gaps in knowledge related to the impact of maternal nutrition on fetal neurodevelopment	
How does preconceptional and gestational nutritional status impact offspring development across the life span?	Longitudinal studies are needed, examining the long term effects of malnutrition on development.
What are the maternal macro- and micronutrient requirements during preconception and pregnancy that promote normal fetal brain development? What are the specific nutritional needs of girls and young women that will promote their own development and set the stage for a healthy pregnancy?	Studies of nutrition requirements of girls and young women beginning in preconception are needed.
What are the best nutrient (micro, macro, and pro- or antiinflammatory) supplements for pregnant women in LRS? What is the effect of these interventions on infant development?	Longitudinal studies to examine effects of both maternal and neonatal nutrient supplements and nutrition on infant growth, stunting, development, and behavior.
How do maternal malnutrition and maternal obesity influence fetal development and birth outcomes?	Prospective studies evaluating the biological pathways by which maternal undernutrition and obesity influence fetal development and birth anthropomorphics.
The social context of the pregnant woman can greatly influence the consequences of insults including malnutrition and inflammation. How does the social context (eg, family support, father support, societal pressures, etc) and maternal stress, anxiety, and depression affect prenatal development? How does the social context ameliorate or exacerbate the effects of malnutrition and inflammation?	Longitudinal studies that include evaluations of stressors and buffers in the environment and how they interact with nutrition and inflammation.
How does dietary inflammation trigger systemic inflammation, particularly during pregnancy?	Intervention studies with long-term follow-up to assess the impact of inflammatory foods and nutrients on outcomes of interest in terms of development.
How do energy requirements change with duration of pregnancy, age, and comorbid infections, such as TB or HIV?	Studies to measure resting energy expenditure in these contexts.
What are useful biomarkers or survey questions to characterize nutritional status?	Assess surveys and biomarkers in various conditions.
2. Gaps in knowledge related to the impact of maternal inflammation on fetal neurodevelopment	
Which neural structures and systems are susceptible to infection and inflammation? When during gestation is the fetus particularly vulnerable?	Studies linking fetal exposure to infection and inflammation to specific areas of neurodevelopment, including timing of exposure.
What are the factors that predispose a fetus to manifest the neurologic effects of viruses including the ZIKV?	Studies examining effects of timing in pregnancy, inflammatory biomarkers, treatments of infected mothers, and newly developed immunizations against viruses, such as the ZIKV.
What are the specific linkages between biomarkers of infection/inflammation and neonatal behavior?	Longitudinal studies to assess ranges of biomarkers during pregnancy and whether these relate in meaningful ways to neonatal outcomes.
How can we develop better inflammatory, stress, and predictive biomarkers?	Longitudinal studies of cytokines and inflammatory biomarkers in urine and plasma throughout pregnancy related to pregnancy outcome and fetal growth.
3. Gaps in knowledge related to the impact of the interaction of maternal nutrition, inflammation, and other influencing factors on fetal neurodevelopment	
Improved analytic methods to investigate the complex web of interacting factors on human development across the life span.	Population-based studies, including preconception, prenatal, perinatal, neonatal, and childhood to adulthood outcomes and use of multilevel modeling techniques.
What is the relationship between the maternal diet and the microbiota and how does this impact the infant microbiota and short- and long-term development outcomes?	Studies of both maternal and infant nutritional intake (including use of breast milk and or formula) and microbiota of both relative to infant outcomes.
How does the placenta moderate and respond to maternal stress, inflammation, and malnutrition?	Studies evaluating mechanisms involved with placental growth, determination of the placental microbiota, and inflammation relative to fetal growth.
How do the prenatal and postnatal environments jointly determine development?	Longitudinal studies to assess effects of both prenatal and postnatal environments. Evaluation of the effects of interventions during each period on growth, behavior, and developmental outcomes.
Effect of environmental toxin exposures, including indoor air pollution, tobacco smoke, biomass fuels, poor sanitation, lead, and pesticides on nutrition, inflammation, and neurodevelopment. Are there interactions of concern? Are repeated exposures additive?	Studies examining exposures prenatally and postpartum on fetal growth and outcomes. Research evaluating the interactions between these different exposures is needed.
What is the impact of antenatal drugs/medications?	Studies examining exposures prenatally and intrapartum on fetal growth and outcomes. In particular, studies are needed that consider the consequences of repeated exposures and of interactions between drugs/medication.
What is the impact of poverty and socioeconomic status on neurodevelopment?	All studies need to consider the impact of poverty on neurodevelopmental outcomes.

TABLE 1 Continued

Problem or Question	Studies Needed
How can we measure and account for individual variability in the stress response?	Studies examining multiple maternal and environmental factors and stressors associated with both adverse outcomes and resiliency.
4. Gaps in knowledge related to evidence-based interventions for optimal fetal neurodevelopment	
What are the technologically appropriate, cost-effective interventions to decrease preterm birth and its morbidity and mortality in LRS?	Examine effects of peer support and counseling on preconception women to increase interpregnancy spacing and decrease morbidity and mortality.
What is the effect of improving preconceptional maternal health on fetal neurodevelopment?	Examine effects of peer support and counseling to enhance maternal preconceptional health and fetal neurodevelopment.
Are there postnatal interventions that improve long-term neurodevelopmental outcomes (eg, nutritional supplementation, caregiving practices)?	Studies assessing the catch-up growth of infants growth restricted at birth who receive various nutrition or feeding interventions. For example, combinations of breast milk with and without nutritional supplementation and kangaroo care or cuddling.
To what extent does delayed cord clamping and placental transfusion affect the rates of iron deficiency and developmental outcome of the term and preterm neonate ?	Studies examining the iron stores, rates of anemia, and outcomes of pregnancies with delayed cord clamping.
How does HIV treatment impact pregnancy outcomes? What are safe and effective means to decrease inflammation in the various conditions?	Longitudinal studies of HIV-infected women from preconception to delivery.

the pregnant woman's environment include maternal and paternal age; marital, social, and employment status; educational attainment; interpregnancy intervals and number of children cared for; exposure to violence, natural disasters, or toxins; access to safe water and hygiene practices; food security and nutritional status; acute and chronic illness (including mental health); medication use; and exposure to or use of tobacco, alcohol, or other drugs. Male partner involvement may positively or negatively influence maternal stress depending on the interpersonal dynamics of the relationship and whether there is exposure to intimate partner violence. Because we are particularly interested in the interplay of nutrition and inflammation on neurodevelopmental outcomes, it must be recognized that many of these maternal factors are also inflammatory (infections, smoking, stress, and pollution among others) and others have an impact that is mediated through nutrition or food security. It is extremely difficult to clearly delineate the direct effect of each concurrent maternal stressor, including the multiple associations with environmental exposures.[75]

One primary consequence of maternal malnutrition, inflammation, and other sources of prenatal stress is a poor birth outcome, such as prematurity or growth restriction. These phenotypes are often used as indications of prenatal adversity.[76] In fact, the original evidence supporting the fetal origins or fetal programming hypothesis, which proposes that "alterations in fetal nutrition and endocrine status result in developmental adaptations that permanently change structure, physiology, and metabolism, thereby predisposing individuals to cardiovascular, metabolic and endocrine disease in adult life," came from epidemiologic studies documenting an association between birth phenotype and future development of physical and mental health problems.[76,77] For example, impaired fetal growth has been linked to later increased risk for cardiovascular disease or type 2 diabetes mellitus.[78] Subsequent experimental and prospective clinical research has found similar vulnerabilities before, during, and after the fetal period, namely, "environmental processes influencing the propensity to disease in adulthood operate during the periconceptual, fetal, and infant phases of life."[78] For example, both cognitive function and insulin secretion in childhood are influenced by the type of feeding of the premature neonate, who is subjected to higher fat intakes than are experienced in utero.[78]

Published rates of prematurity in LMIC range from 5% to 25%.[79] Because one-third of infants globally are born at home, rates are likely to be significantly higher, especially in LRS.[79] Because resources and training for appropriate management of preterm or very LBW infants are limited in LMIC, the outcomes in these settings are likely to be more often associated with increased morbidity and mortality.[61] This context supports the enormity of the problem of preterm birth globally.

The global burden of neurodevelopmental consequences of intrauterine and neonatal insults was evaluated recently in a comprehensive review by Mwankiki and colleagues.[80] This review of over 150 studies illustrated that the median risk of at least 1 major consequence of early life stress was 39.4%. Among a wide range of outcomes, the most common impairments were learning difficulties, developmental delay, cognitive impairments, and sensory deficiencies. This important article provides evidence that intrauterine and neonatal insults

result in significant long-term neurodevelopmental impairments and have a high likelihood of affecting more than 1 domain. Not only did this analysis highlight the global significance of the consequences of early life insults, it also revealed that there are relatively few high-quality studies in this area of research.

Prenatal inflammation, malnutrition, and maternal psychological distress contribute significantly to both fetal growth restriction and preterm birth.[81] Neurodevelopmental impairments are prevalent among infants affected by prematurity, LBW, and IUGR, including cognitive impairments and psychiatric dysfunction.[82] In a recent prospective, longitudinal evaluation, very preterm children were 3 times more likely to meet criteria for any psychiatric disorder compared with their term counterparts at 7 years of age.[83] Importantly, the association between gestational length and neurodevelopment is present even among children born in the late preterm and early term periods.[84] During infancy, fetal growth restriction in both term and preterm infants is associated with irritability, constant crying, feeding difficulties, jitteriness, and hyperreactive responses to noise, change of posture, or bathing.[85] During childhood and adolescence, fetal growth restriction is associated with attention-deficit/hyperactivity disorder, anxiety, depression, internalizing and thought problems, poor social skills, and autism spectrum disorder.[81] Stunting (ie, significant impairment of linear growth), which is highly prevelant in LMIC (eg, in India, Pakistan, and Guatemala; by the time of weaning, 40%–50% of infants are stunted[63,86–88]) has particularly debilitating effects on neurodevelopment. Evidence that prematurity and growth restriction have pervasive and long-lasting effects on health is irrefutable. Much less is known about the biological processes and mechanisms that regulate fetal development and negatively influence later health. This is especially the case in LMIC, and there is a clear need for prospective and longitudinal research evaluating the biological mechanisms by which nutrition and inflammation lead to neurodevelopmental impairments.

The vast majority of prospective studies evaluating prenatal maternal distress and child neurodevelopment have been conducted in high-resource countries. Thus, the global health burden is likely underestimated. Recently, prospective studies, primarily conducted in high-income countries, have begun to elucidate the psychological and biological processes during the prenatal period that contribute to these neurodevelopmental outcomes. Depression is perhaps the most well studied psychological process among women of childbearing age and is often accompanied by anxiety as well as high levels of stress and exposure to adverse life events. Globally, depression is a leading cause of disease-related morbidity among women, and its prevalence is twofold greater than that in men.[89] Fetal exposure to maternal psychological distress, including anxiety, stress, and depression, is associated with cognitive delays, dysregulated stress responses, and greater negative emotionality during infancy and childhood and contributes to the risk of the development of psychopathology later in life.[90] Prospective evidence indicates that prenatal maternal distress increases the risk for poor executive functioning, attention-deficit/hyperactivity disorder, and the development of internalizing and externalizing problems during childhood.[91,92] Importantly, these studies illustrate consequences of prenatal stress beyond any effects of the postnatal environment.

The impact of maternal distress is likely more severe in LRS. Rates of depression in the perinatal period are higher in LRS (31%) compared with resource-sufficient settings (21%). Immigrants and women of low socioeconomic status and/or who experience trauma, including natural disasters, are at particularly high risk.[93] These research findings demonstrate the profound global health impact of prenatal maternal depression on both maternal and child health.

An additional potential mediator of maternal and infant health that impacts nutritional status, inflammation, and the environment is the health of the intestinal microbiome.[94] The microbiome maintains the homeostasis of the normal flora of the human gut, which varies widely by age, region, diet, health status, and environment. Even the placenta has a distinctive microbiota.[95] A healthy microbiome has more diversity and richness than an unhealthy microbiome. The microbiome evolves over the course of pregnancy, with beneficial changes in healthy, well-nourished pregnant women.[96] At the time of birth, the infant's microbiome differs depending on the placental microbiome characteristics and whether the birth was vaginal or by cesarean delivery.[97–99] The breastfed infant has a microbiome with a greater proportion of lactobacillus than that of infants who are formula fed.[100,101] The microbiome continues to evolve over the first 2 years of life, with a more adultlike microbiota present at 24 months.[102] It is not known what alterations occur in the microbiome of women in LRS who may have multiple comorbid illnesses. To date, there is compelling evidence that characteristics of the microbiota are associated with being overweight and obesity,[103] and that the microbiome varies for HIV-infected and -uninfected individuals[104]

and likely with enteric and other infections. Exactly how any of this impacts the neurodevelopment of infants and children remains unclear.

IMPLICATIONS FOR RESEARCH, PROGRAM, AND POLICY DEVELOPMENT

Table 1 summarizes recommendations for addressing research gaps and studies needed to better understand the interactions among maternal nutrition, inflammation, and other influencing factors and the resulting impact on fetal neurodevelopment. From the perspective of policy, in the current research funding system, challenges exist for what questions can be investigated and how studies can be designed. Because the typical funding cycle is 4 to 5 years on average, it can be extremely difficult to recruit and maintain the long-term cohorts required to answer developmental questions over the life span, particularly when trying to understand associations between exposures and conditions in the prenatal or early infancy stages and outcomes in adults. Given the critical need for high-quality evidence in this area to guide program and policy decisions at local, regional, and global levels, multidisciplinary involvement from key stakeholders, including funding agencies, is essential.

ABBREVIATIONS

CMV: cytomegalovirus
CNS: central nervous system
IUGR: intrauterine growth restriction
LBW: low birth weight
LMIC: low- and middle-income countries
LRS: low-resource settings
TB: tuberculosis
ZIKV: Zika virus

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