Chapter 10
Assessing the Effects of Maternal Anemia on Child Development in Benin

Florence Bodeau-Livinec, Michel Cot, Ghislain K. Koura, and Michael J. Boivin

10.1 Background

10.1.1 Burden of Anemia in Pregnancy

In developing countries, over 50 % of pregnant women are anemic (WHO 1998). Thirty to fifty percent of these women have iron-deficiency anemia (IDA) compared with a much lower prevalence of IDA among pregnant women in developed countries where diets and iron supplementation are better (MMWR PiCD 1990). Maternal anemia as it affects child development is an excellent illustration of the interconnected feed-downward (culture- and context-driven) and feed-upward

F. Bodeau-Livinec, M.D., Ph.D. (✉)
IRD UMR 216, Mère et enfant face aux infections tropicales, Paris, France

Faculté de Pharmacie, Université Paris Descartes, Paris, France

Ecole des Hautes Etudes en Santé Publique, Rennes, France
e-mail: florence.bodeau-livinec@ehesp.fr

M. Cot, M.D., Ph.D. • G.K. Koura, M.D., Ph.D.
IRD UMR 216, Mère et enfant face aux infections tropicales, Paris, France

Faculté de Pharmacie, Université Paris Descartes, Paris, France
e-mail: michel.cot@ird.fr; kourakobtoghislain@yahoo.fr

M.J. Boivin, Ph.D.
Departments of Psychiatry and Neurology/Ophthalmology, Michigan State University, 965 Fee Road, Room A227, East Lansing, MI 48824, USA

Neuropsychology Section, Department of Psychiatry, 2101 Commonwealth Blvd, Suite C, Ann Arbor, MI 48105, USA
e-mail: boivin@msu.edu

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(neurobiology-driven) interactive processes and developmental plasticity that are at the core of the co-constructivist approach (Li 2003). In other words, the environmental/cultural context contributes to maternal anemia, subsequently shaping the child's brain/behavior development across the life-span (pre- and postnatally). Maternal anemia affects the child initially in terms of the gestational neurobiological environment for the child in utero, then in maternal health and quality of care giving in infancy and early childhood, and following into middle childhood through household nutritional and parasitic risk factors that contribute to the mother's chronic anemia, which extend to the child as he or she grows into adulthood. For women, these co-constructivist dynamics extend across generations as the developing girl, herself, later becomes a chronically anemic mother.

10.1.2 Physiopathology in Pregnancy

During pregnancy, the amount of iron required to increase the red cell mass, expand the plasma volume, and allow for the growth of the fetal-placental unit increases significantly. Oxygen-carrying capacity is proportional to the circulating hemoglobin concentration. From a physiologic perspective, the evidence is clear that moderate anemia is undesirable (Yip 2000).

10.1.3 Risk Factors for Anemia in Pregnancy

Malaria and iron deficiency are important and well-known risk factors for anemia during pregnancy. It is estimated that 26 % of severe anemia among pregnant women can be attributed to malaria and around 50 % to iron deficiency. The prevalence of fetal anemia at birth is high in malaria-endemic areas, and the risk is associated with the presence of high-density parasitemia in the mother at delivery. Other risk factors include helminth infections with hookworms and schistosomas, multiple pregnancy, urinary tract infection, sickle cell disease, micronutrients deficiency (folic acid), under nutrition, and poor antenatal care (Geelhoed et al. 2006). Our study in Benin, which is a small Francophone country in West Africa that is very impoverished, confirmed the role of these factors (Ouédraogo et al. 2012). Relationships between iron deficiency (ID) and infections are unclear, as is the role of specific infections (malaria, hookworm, urinary tract infection, bacterial vaginosis). The risk of iron-deficiency anemia is increased with parity: nearly threefold higher for women with 2–3 children and nearly fourfold greater for women with four or more children (Looker et al. 1997). The following genetic factors may be risk factors for anemia: hemoglobin C trait found in 10 % of Beninese people and sickle cell disease found in 4 % of Beninese newborns. The prevalence of sickle cell trait is 22 % in Cotonou in Benin (Latoundji et al. 1991).

10.1.4 Consequences of Anemia and ID in Pregnancy on the Outcomes in Children

10.1.4.1 Preterm Delivery and Low Birth Weight

Early anemia has been associated with an increased risk of preterm delivery (Xiong et al. 2000; Scanlon et al. 2000). Allen suggested three potential mechanisms whereby maternal IDA might give rise to preterm delivery: hypoxia, oxidative stress, and infection (Allen 2001). Chronic hypoxia from anemia could initiate a stress response, followed by the release of corticotropin-releasing hormone (CRH) by the placenta, increased production of cortisol by the fetus, and an early delivery. Some studies, including our study in Benin, have shown a link between anemia during pregnancy and preterm and low birth weight babies (Bodeau-Livinec et al. 2011; van den Broek 2003). No study, to our knowledge, however, has investigated the long-term outcomes of these children.

10.1.4.2 Anemia and ID in the Fetus

Results regarding maternal hemoglobin concentrations at or near term and cord blood hemoglobin concentrations are not consistent (Allen 2000; Brabin et al. 2004). Evidence, largely collected among infants aged 6–12 months, is accumulating that children born to anemic mothers have lower iron stores, even when they are born at term and with a normal birth weight (Strauss 1933; Colomer et al. 1990; Kilbride et al. 1999; Morton et al. 1988; Preziosi et al. 1997; Ahmad et al. 1983). It is known that iron is preferentially allotted to red blood cells. When iron supply is insufficient, the fetal brain may be at risk, even if the infant is not anemic (Lozoff and Georgieff 2006). In pre-anemic pregnant women, low ferritin concentrations also correlate with lower serum ferritin concentrations in the neonate (Lao et al. 1991). Iron deficiency can be remedied at any point; its consequences, however, cannot. According to Allen, more studies that assess the relationship between the iron status of pregnant women and the iron status of their infants postpartum are needed. Maternal anemia and subsequent infant health and development also deserve further study.

10.1.4.3 Cognitive Outcomes and Mental Health

In infants and preschool children, iron-deficiency anemia results in developmental delays and behavioral disturbances (decreased motor activity, social interaction, and attention to tasks) (Pollitt 1993; Idjradinata and Pollitt 1993). In South Africa, Perez et al. (2005) found that infants whose mothers were anemic in the early postpartum scored worse on developmental tests at 10 weeks and 9 months of age compared

with infants whose mothers were not anemic. In the USA, Tamura et al. found an association between fetal iron status (umbilical cord serum ferritin concentrations) and lower scores on mental and psychomotor development test (Tamura et al 2002). Recent studies suggested a potential impact of maternal iron deficiency during pregnancy on a child's mental health and cognitive outcomes, but none showed an association (Insel et al. 2008; Hernandez-Martinez et al. 2011; Mihaila et al. 2011; Christian et al. 2010). To our knowledge, data related to maternal anemia and infant behavior is limited (Vaughn et al. 1986).

Given the potential huge impact of anemia and ID during pregnancy on childhood outcomes and the lack of data, we proposed our present developmental assessment research program. Our study in Benin follows children of 12 months of age in order to evaluate these relationships between maternal anemia, ID, and subsequent developmental outcomes for the children.

10.2 Hypothesis

The central hypothesis in our research program is that anemia in pregnancy and maternal iron deficiency are associated with adverse developmental outcomes and that the degree of anemia is associated with the degree of adverse outcomes. Possible mechanisms are decreased brain development due to iron deficiency, through the higher risk of low birth weight (LBW) and preterm births, through a higher risk of anemia and iron deficiency at birth linked to poorer developmental and mental health outcomes, or through hypoxia in pregnancy (severe and/or chronic).

10.3 Objectives

Our goal is to examine the cognitive function of children as a result of anemia in pregnancy. Lower scores on cognitive assessment are expected with decreasing levels of hemoglobin, adjusting for pre- and postnatal factors known to be associated with cognitive function in childhood.

10.4 Methods

10.4.1 Study Design

The study included a follow-up by 12 months of age of children born in Benin within a multi-country randomized controlled trial (RCT) funded by the European Commission (MiPPAD project). Offspring from the first 1,005 pregnant women

enrolled in this RCT comparing mefloquine (MQ) and sulfadoxine-pyrimethamine (SP) for intermittent preventive treatment for malaria during pregnancy (IPTp) are assessed.

10.4.2 MiPPAD Trial

The main outcome studied was low birth weight. The pregnant women were recruited from January 2010 to May 2011. All pregnant women who attended an antenatal care visit (ANC) during the second trimester of pregnancy were invited to participate. The exclusion criteria included psychiatric disease, neurological disease, or HIV infection. With informed consent, pregnant women were randomly assigned to either SP or MQ. If the gestational age at this visit coincided with the fundus being palpable (at least 13 weeks of gestation), the first dose of IPTp (either SP or MQ) was administered. The second dose of SP/MQ was administered coinciding with the next ANC visit at least 1 month after the previous dose. All IPTp doses were administered under supervision.

10.5 Variables

10.5.1 Variables Recorded in 1,005 Pregnant Women

At the time of recruitment, parity, maternal age, gestational age (date of last menstrual period and uterine height), gravidity, history of previous preterm birth, low birth weight, miscarriage, and stillbirth were recorded. Socioeconomic status including variables such as supplied latrines, supplied electricity, mother's education level, father's education level, marital status, and literacy (reading, writing) were recorded. The mothers were screened for sickle cell disease and hemoglobin C trait using electrophoresis. Three times during pregnancy (at the first IPTp administration, at the second IPTp administration, and at delivery), blood samples of the cohort women were evaluated for hemoglobin concentration (Hb), serum ferritin, C-reactive protein (CRP), folic acid, vitamin B_{12}, and malaria (parasite density and placental malaria). Anthropometric measurements for pregnant women were recorded at each visit: weight and height at first ANC to calculate the BMI, weight at each antenatal visit, and total weight gain during pregnancy. Helminths (ankylostomiasis, especially prevalent in Benin) were systematically searched with the KATO test. Other pregnancy complications recorded were mortality, urinary tract infection, hemorrhage during pregnancy, and other infections. The number of antenatal care visits was recorded. Anemia was defined as severe (Hb < 80 g/l), moderate (Hb ≥ 80 and <100 g/l), mild (Hb ≥ 100 and <110 g/l), and no anemia (Hb ≥ 110 g/l).

10.5.2 Variables in Infants at Birth, 1, 9, and 12 Months in Offspring

At delivery, newborns were weighed and measured and their gestational age assessed by the Ballard score (Ballard et al. 1991). Birth defects and infant's gender were recorded.

Children follow-up is ongoing. Anthropometric measurements in infants are assessed at 1, 9, and 12 months, including child weight (measured in kg), length (measured in cm using a measuring board), mid-arm circumference, and head circumference (measured in cm using a measuring tape).

Blood samples in infants at birth, 1, 9, and 12 months of age are collected to assess Hb and malaria. Additional blood samples may be collected in case of emergency. Additional assessments of serum ferritin, CRP, and blood lead are performed at 12 months. Sickle cell disease and hemoglobin C are sought by electrophoresis. At 12 months of age, motor and cognitive functions are evaluated according to the Mullen Scales of Early Learning (MSEL). Mothers are asked about their child's potential deficiencies through the ten questions questionnaire (TQQ). Nutrition in infants, especially breastfeeding, is assessed through a questionnaire. At 1 year of age, anemia is defined as Hb concentration <110 g/l [34].

10.5.3 Variables in Mothers When Offspring is 1 Year of Age

Maternal depression is evaluated when offspring is 1 year of age through the Edinburgh Postnatal Depression Scale, which was already in use in Uganda (WHO/UNICEF/UNU 1997; Caldwell 2001). Maternal interaction with the child is evaluated through the use of the HOME inventory subscales (Caldwell 2001). Maternal nonverbal IQ is collected at 1 year postpartum through the Raven's Progressive Matrices Test.

10.6 Preliminary Findings

Our findings after the assessment of approximately 320 one-year-old children at the midway point of our follow-up data collection are very preliminary. However, we are seeing a clear and significant association between impaired development and both environmental and care giving quality risk factors. At this point maternal depression does not seem to be related to child Mullen outcomes at 1 year of age. This conclusion is based on a preliminary evaluation of overall child cognitive ability as measured by the Mullen Early Learning Scales composite score as it relates to maternal cognitive ability (Raven's Progressive Matrices Test), quality of care giving (Caldwell HOME scale), and SES (physical quality of the home).

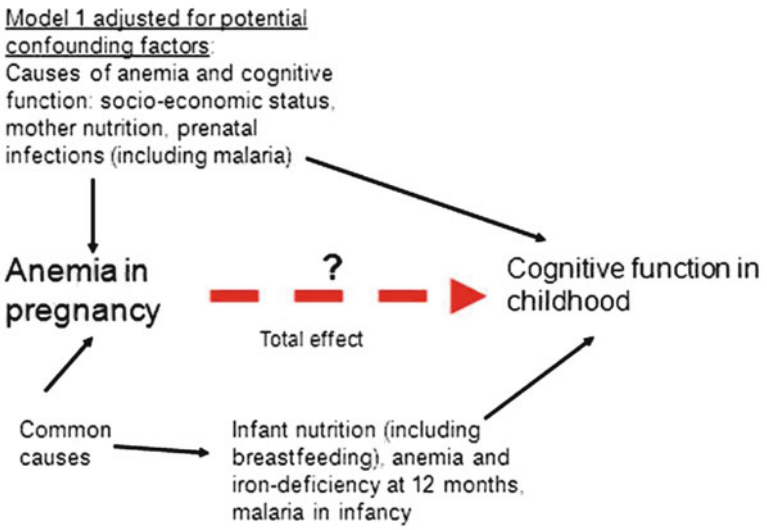

Fig. 10.1 DAG for the total effect of anemia in pregnancy on cognitive function in childhood

When all follow-up data has been completed, we will use the directed acyclic graph (DAGs) as developed by Hernan and others (Hernan et al. 2002). Within this strategy of analysis, causal diagrams will be used and will consider a priori causal knowledge. The role of each factor in relation to the exposure (anemia) and the outcome (cognitive function) will be considered according to a priori assumptions about the underlying biologic mechanisms. The role of covariates may include confounding, mediating, or effect modification. The analysis will be adapted accordingly as described below.

To study the total effect of anemia in pregnancy on cognitive development, we will take into account potential confounding factors [model 1 (Fig. 10.1)]. Important variables will be considered as adjustment factors (potential confounding) in the final analyses and will include lead exposure (found to be significant in a preliminary sample of our children); malaria during pregnancy; maternal malnutrition; micronutrient deficiencies (iron, vitamin B_{12}, folic acid); socioeconomic status; maternal age; gravidity; number of antenatal care visits; hemorrhage during pregnancy and other pregnancy complications; other infections in pregnancy, especially helminthes and urinary infections; nutrition in infancy (including breastfeeding); malaria during the first year of life; and iron deficiency at 12 months. Of note, the variables preterm birth, LBW, and anemia at birth and in infancy might be confounding factors as they may share common causes with anemia (Calis et al. 2008; Bodeau-Livinec et al. 2011; Berkowitz and Papiernik 1993; Siza 2008) during pregnancy and are risk factors for poor cognitive development (Walker et al. 2007). We will adjust for these common causes (socioeconomic malaria during pregnancy,

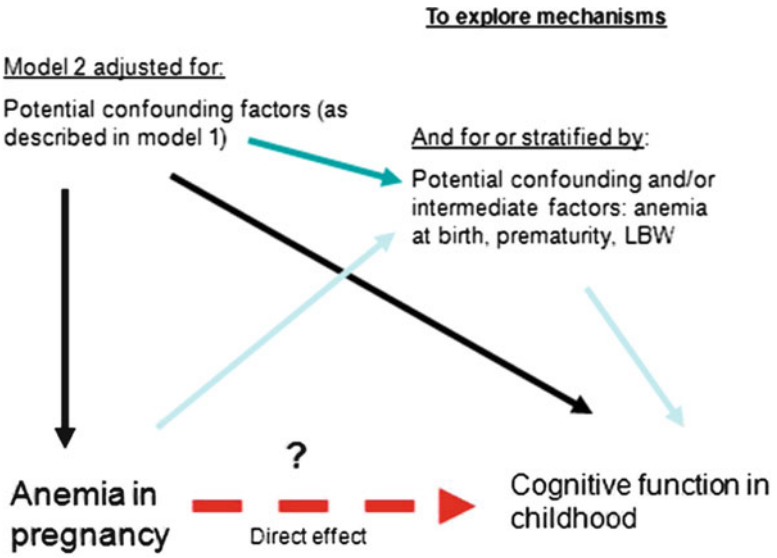

Fig. 10.2 DAG for the direct effect of anemia in pregnancy on cognitive function in childhood

maternal age, gravidity, number of antenatal care visits, maternal nutrition, maternal BMI), in order to remove possible confounding.

To study the direct effect of anemia in pregnancy on cognitive development, in addition to the variables adjusted for in model 1 (Fig. 10.1), we will take into account potential intermediate factors that may be in the causal pathway between anemia during pregnancy and cognitive outcome [model 2 (Fig. 10.2)]. The variables preterm births, LBW, and anemia at birth and in infancy may be intermediate factors, because they may be in the causal pathway between anemia during pregnancy and cognitive function later in childhood. Anemia during pregnancy may be a risk factor for preterm birth, LBW, and anemia at birth and in infancy (Colomer et al. 1990; Bodnar et al. 2005; Koura, personal communication). All of these factors are risk factors for poor development in childhood (Walker et al. 2007). If we find a relationship between these variables (anemia at birth and in infancy, preterm birth, low birth weight) and first, anemia during pregnancy and second, cognitive function, we will consider them as potential intermediate factors. Comparing models adjusting for preterm birth, LBW, and anemia in infancy to models excluding them will give us some insight into mechanisms. For instance, if estimates are different in the two models (model 1 in the DAG above adjusted for socioeconomic factors, malaria during pregnancy, maternal age, gravidity, number of antenatal care visits, maternal nutrition, BMI, prenatal infections and model 2 adjusted for the same factors and LBW that is assessing the direct effect of anemia during pregnancy on cognitive function in infancy), it could mean that LBW is an intermediate factor in the pathway between maternal anemia and cognitive outcome. If these estimates

are not different in these two models, it could mean that LBW is not an intermediate factor (Bodnar et al. 2005). The same strategy applies to other potential intermediate factors.

We will also use another method to explore preterm births, LBW, and anemia at birth and in infancy as intermediate factors. We will apply model 1 in the following subpopulations: term babies weighing more than 2,500 g at birth, expected to be 82.7 % of our sample, and babies with anemia at birth, expected to be 61.1 % of our sample. This may provide information about the direct effect of anemia during pregnancy on cognitive function at 1 year of age in these populations. The same strategy will apply to study the association between iron-deficiency anemia and child development.

10.7 Possible Interventions and Conclusions

Various interventions have been proposed to improve early child development in low-income countries. The majority consist of parenting interventions in the postnatal preschool period that promote interactions between the children and their parents in the fields of education, learning, and feeding (Engle et al. 2011). Although the problems of intrauterine growth restriction (IUGR) and exposure to toxic agents (e.g., lead) and parasitic diseases (mainly malaria in endemic areas) have been identified as risk factors for impaired child development, very few interventions have been attempted involving pregnant women, and to our knowledge, none of these have specifically evaluated the impact of existing measures to prevent maternal anemia on child development.

Presently, following WHO recommendations (WHO 2001), a policy of micronutrient supplementation (iron and folic acid) is made available to all pregnant women in the majority of Sub-Saharan African countries. In Benin, as in most malaria-endemic areas, IPTp with sulfadoxine-pyrimethamine is also given twice in the course of pregnancy, along with the distribution of insecticide-treated bednets at the first antenatal visit. National guidelines also recommend that women should be systematically given an antihelminthic treatment with mebendazole at the same time as IPTp intakes. Such measures, if correctly implemented, should logically improve both the hematological status of the women and the cognitive development of their children. However, it is not clear if some of these interventions might be detrimental for child development. For example, supplementation of children with iron and folic acid has been shown to be detrimental in populations with high rates of malaria transmission, because iron given to non-anemic children may induce favorable conditions for the parasite multiplication and an increased risk of severe illness in supplemented children (Sazawal et al. 2006).

As a wide panel of prevention measures are already applied to pregnant women in low-income countries to decrease the burden of anemia, one of the main priorities for future research would be to evaluate carefully the effects of these interventions (both protective and potentially detrimental) in reducing developmental impairment

in the children (Walker et al. 2011). It will then be the time to conclude on the role of maternal anemia (and specifically iron-deficiency anemia) on child development and to propose new interventions in pregnancy with broader objectives, including the prevention of IUGR.

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