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INTEGRATED STRATEGIES NEEDED TO PREVENT IRON DEFICIENCY AND TO PROMOTE EARLY CHILD DEVELOPMENT

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Abstract

Iron deficiency (ID) and iron deficiency anemia (IDA) are global public health problems that differentially impact pregnant women and infants in low and middle income countries. IDA during the first 1000 days of life (prenatally through 24 months) has been associated with long term deficits in children's socio-emotional, motor, cognitive, and physiological functioning. Mechanisms linking iron deficiency to children's development may include alterations to dopamine metabolism, myelination, and hippocampal structure and function; as well as maternal depression and unresponsive caregiving, potentially associated with maternal ID. Iron supplementation trials have had mixed success in promoting children's development. Evidence suggests that the most effective interventions to prevent iron deficiency and to promote early child development begin early in life and integrate strategies to ensure adequate iron and nutritional status, along with strategies to promote responsive mother-child interactions and early learning opportunities.

Keywords

maternal iron deficiency; infant iron deficiency; mother-child interaction; maternal depression; caregiving

Introduction

Iron deficiency (ID) and iron deficiency anemia (IDA) are major public health problems during pregnancy and infancy in most low and middle income countries [1,2]. Although rates of IDA have declined in high income countries, iron deficiency remains a concern in the USA during pregnancy and infancy [3,4]. National estimates of ID during pregnancy based on the National Health and Nutrition Examination Survey (NHANES) are 18%, with anemia at 5.4% [3]. In contrast, in India, the national rate of anemia (primarily IDA) among pregnant women is 65–75% [5]. Causes of ID/IDA are thought to be inadequate intake of dietary iron, poor bioavailability of dietary iron from fiber and phytate-rich diets, and increased iron requirements during pregnancy. National data from India indicate that among

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young children, rates of ID are increasing, with the most recent rates among 12–23 month old children at 80% [6].

Infant Iron Requirements

Infants born to mothers with IDA are at risk for ID [7] and potentially at risk for low brain maturation, especially when coupled with prematurity [8]. The effects of low prenatal iron appear to contribute to poor performance on tests of language comprehension and the inability to follow directions over at least the first five years of life, as shown in a follow-up of children with umbilical cord serum ferritin concentrations <76 mg/L [9]. The first 1000 days of life (prenatal and through 24 months) include high nutritional demands to support the rapid growth and development that occur during this period (see Figure 1) [10]. The Institute of Medicine estimates that full-term infants have adequate iron stores for the first 4–6 months, with a dietary iron requirement of 0.27 mg/day, well within the average iron content of breast milk [7]. During the second 6 months of life, the depletion of prenatally acquired iron stores, together with rapid development and high nutritional demands, increase the iron requirement to 11 mg/day [7]. Not only is this level beyond what is available from breast milk, but complementary foods are often low in iron, making 6–12 month-old infants vulnerable to ID. After 12 months, the iron requirement drops to 7 mg/day through age 3 years [7]. Young children who consume an iron-rich diet can meet this requirement.

Iron Deficiency and Child Development

ID has been linked to delays in socio-emotional, cognitive, motor, and neurophysiological functioning [11,12]. ID often occurs in the context of other nutritional deficiencies as well as social and environmental challenges, such as poverty and family stress, making it difficult to isolate the effects of ID. Chronic iron deficiency may alter dopamine metabolism, myelination, and hippocampal structure and function, including long-term genomic changes [13]. Both animal studies [13] and longitudinal follow-up studies of children who experienced ID early in life [14] have suggested that the irreversibility of chronic ID prior to 24 months is plausible, but not confirmed.

Mechanisms Linking Iron Deficiency and Child Development

Although there is not conclusive evidence regarding the direct effects of iron on children's development, one possibility is through the neurotransmitter system, particularly dopamine metabolism [15]. Dopamine clearance has strong effects on attention, perception, memory, motivation, and motor control; low iron may affect these functions by interfering with myelination and dopaminergic function [15].

Another possibility is that there may also be indirect effects of iron deficiency on children's development. The hesitation and wariness associated with ID may make children less able to evoke and benefit from the social and environmental opportunities necessary to facilitate early development. Alternatively, mothers of children with ID may also be ID, because they often share the same diet [16,17]. Mothers with ID are less responsive than iron-sufficient mothers [16] and potentially less able to provide stimulating caregiving behavior.

Maternal Iron Deficiency

A recent review reported evidence linking ID with maternal depressive disorders [18]. Evidence for a pathway linking ID with maternal depressive disorders comes two studies. One showed an association between low maternal hemoglobin status and postpartum depression among USA mothers (n=37) [19] and the other was a randomized controlled trial among 64 mothers with IDA in South Africa; mothers who received iron supplements showed improvement in depression, stress, and parent responsivity [20–22]. Although these studies suggest an association between ID and depression, they were conducted in settings where rates of IDA among pregnant women are relatively low (South Africa 9–12% and USA 5.4%) [23,24], raising concerns that women with IDA may be unique in other ways that relate to their children's development, such as poverty. Additional research is needed to understand how maternal iron deficiency is associated with care giving behavior.

ID has been linked to depression through neurotransmitter pathways, particularly dopamine [25], raising the possibility that high rates of maternal depression in low and middle income countries may be partially attributable to the high rates of ID/IDA. Behavioral interaction patterns, such as maternal sensitivity and responsivity also operate through dopaminergic pathways [26], raising the possibility that the association between maternal depression and poor caregiving behavior may be partially attributed to maternal ID/IDA.

Maternal Depressive Disorders

Depressive disorders are common causes of morbidity throughout the world [27]. The World Health Organization estimates that by 2020, depression will be the second largest cause of disability adjusted life years across all ages and both genders [28]. Rates of perinatal depressive disorders are particularly high in low and middle income countries, where they are often associated with poverty and gender disparities [29].

The symptoms associated with perinatal mood disorders, including lethargy, difficulty with concentration, and lack of attention to daily tasks can compromise women's caregiving behavior [29,30]. Depressive disorders during pregnancy and throughout the first year of parenting are relatively common among women in low and middle income countries, affecting 15–57% of mothers and comprising approximately 14% of the global burden of disease [27]. Not only do depressive disorders interfere with maternal functioning and caregiving behavior, they often extend to the next generation, compromising infants' growth and development [29]. With extremely limited options for treatment [29, 31], millions of women begin parenting with depressive disorders [32, 33].

In a recent meta-analysis of maternal depressive disorders and early childhood growth, maternal depressive disorders had negative effects on children's early growth, particularly stunting, an indicator of chronic nutritional deficiencies [34] that is often associated with unresponsive care giving practices. Maternal depressive mood has also been associated with delays in children's cognitive development among Bangladeshi children, mediated through unresponsive care giving practices [35]. Findings linking both nutrition and care giving to children's early growth development argue for the integration of nutritional supplemental programs with early home visiting and stimulation programs to ensure that children have both the nutrients they need early in life and the care giving opportunities to practice the skills they are acquiring.

Iron Supplementation/Fortification

The World Health Organization recommends that in countries where rates of ID are high and young children do not have access to iron-rich food (either through lack of availability, severe poverty, or religious or cultural tradition), direct methods, including supplementation and/or fortification be implemented to prevent ID [36]. Although in observational studies, iron deficiency has been associated with mental and motor deficiencies [11,12,37], findings from supplementation trials have not been consistent. Two reviews on iron supplementation among children under 36 months found no effects on early mental performance; a recent meta-analysis of five iron supplementation trials [38] and a Cochrane review of short-term iron supplementation [39] .

Two follow-up studies of school-age children (age 7–9 years) who received iron + zinc supplementation during infancy showed no long term effects on cognition [40,41]. In one study from Thailand, iron + zinc supplementation was given for 6 months beginning at 4–6 months of age and cognitive functioning was measured with global measures and school performance [40]. In the other study from Nepal, iron-folic acid or zinc was given to 12–36 month old children who had participated in an antenatal supplementation trial of iron or zinc, separately, and in combination [41]. The middle-childhood evaluation included general measures of cognition, along with specific measures of executive functioning and motor development, with no effects of the antenatal supplementation.

In contrast, three follow-up studies of children who received iron supplementation prenatally and/or during infancy have shown long term effects on cognition. In a 7–9 year follow-up of children whose mothers received micronutrients during and shortly after pregnancy, there were beneficial effects of iron-folic acid supplementation on children's working memory, inhibitory control, and fine motor functioning [42]. In a second example, a study from China provided iron supplements with the goal of correcting the iron status of infants with iron deficiency anemia (IDA). Children whose iron deficiency was corrected prior to 24 months did not differ in socio-emotional skills at age 4 years from children who had never experienced iron deficiency [43]. Finally, a randomized trial of early home intervention in Chile recruited children with and without IDA at 6 or 12 months of age and followed them until age 10 years [44]. Early iron supplementation and home intervention had beneficial effects on children's cognitive performance. These findings suggest that there may be long term beneficial effects of early iron supplementation, particularly when children's iron deficiency is corrected and when they are in a stimulating environment.

At least two intervention trials highlight the importance of considering the caregiving environment and the household context when evaluating the effects of micronutrient supplementation on children's development. In Jamaica, the beneficial effects of a zinc supplementation trial on motor development were apparent only in the context of an early stimulation intervention [45], presumably because the children had opportunities to practice the skills they were acquiring. Similarly, the trial conducted in Chile [44] included both iron supplementation and a home intervention.

Conclusions

ID and IDA are major public health problems that can have life-long negative consequences on children's development. Evidence suggests that the sequelae of ID may be compromised by maternal depressive symptoms and unresponsive care giving behavior, which may be secondary to maternal ID. Interventions that integrate iron supplementation and early caregiving opportunities have been recommended as ideal strategies to promote early child development; however evidence on the efficacy of integrated interventions is limited. Future integrated trials are needed to evaluate whether intervention strategies that ensure both adequate iron status for young children and opportunities for early learning and responsive care giving are successful in promoting early child development.

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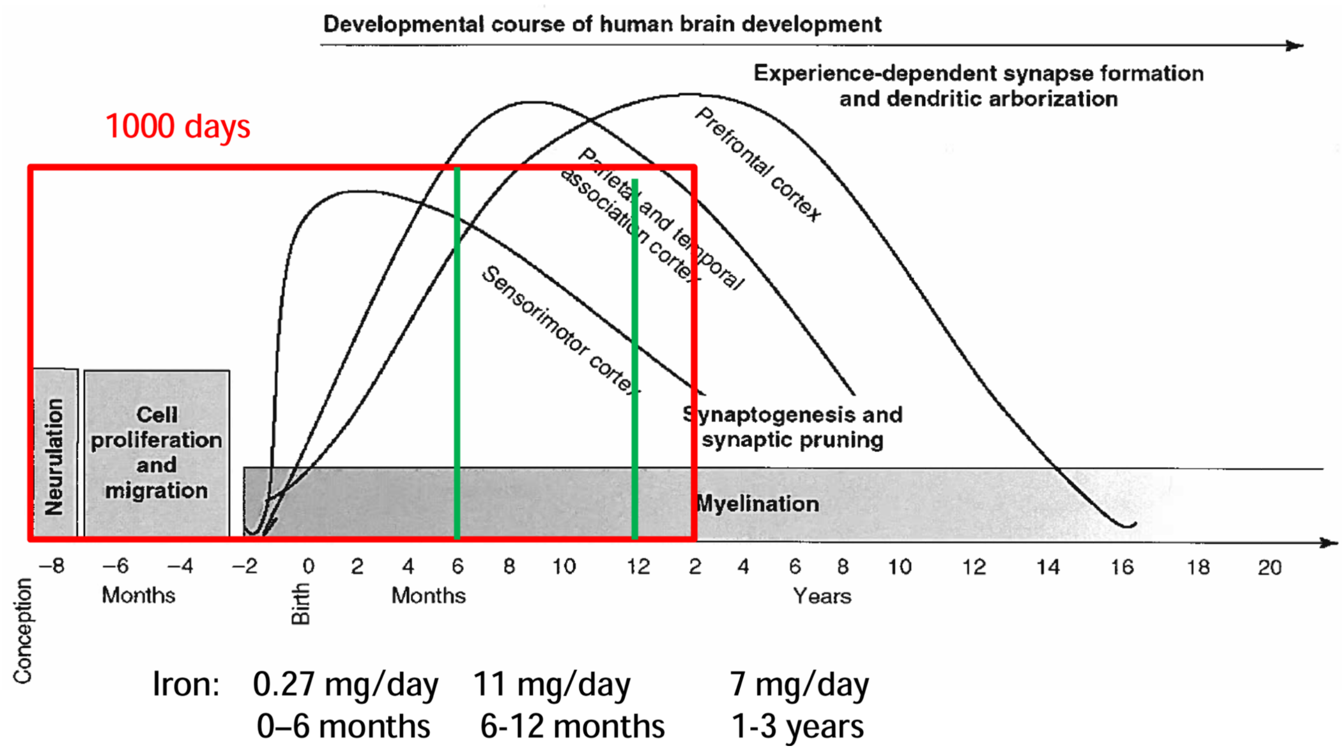

Figure 1.
Early brain development, the first 1000 days, and iron requirements, adapted from Thompson and Nelson, 2001 [10].