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Effects of prenatal and/or postnatal supplementation with iron, PUFA or folic acid on neurodevelopment: update

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Abstract

Neurodevelopment has been linked, among other factors, to maternal and early infant diets. The objective of this review, which is part of the NUTRIMENTHE research project 'The effect of diet on the mental performance of children' (www.nutrimenthe.com), was to update current evidence on the effects of nutritional interventions such as iron, folic acid or *n*-3 long-chain polyunsaturated fatty acid (LCPUFA) supplementation during pregnancy and/or in early life on the mental performance and psychomotor development of children. In May 2014, we searched MEDLINE and The Cochrane Database of Systematic Reviews for relevant studies published since 2009. The limited updated evidence suggests that iron supplementation of infants may positively influence the psychomotor development of children, although it does not seem to alter their mental development or behaviour. The use of multivitamin-containing folic acid supplements during pregnancy did not benefit the mental performance of the offspring. Evidence from randomised controlled trials (RCT) did not show a clear and consistent benefit of *n*-3 LCPUFA supplementation during pregnancy and/or lactation on childhood cognitive and visual development. Caution is needed when interpreting current evidence, as many of the included trials had methodological limitations such as small sample sizes, high attrition rates, and no intention-to-treat analyses. Taken together, the evidence is still inconclusive. Large, high-quality RCT to assess the effects of supplementation with iron, LCPUFA or folic acid are still needed to further clarify the effects of these, and other nutrients, on neurodevelopment. Recent recommendations from scientific societies are briefly presented.

Key words: Iron: PUFA: Folic acid: Neurodevelopment

Background

Neurodevelopment has been linked, among other factors, to maternal and early infant diets. Previously, within the research project 'The effect of diet on the mental performance of children' (NUTRIMENTHE, www.nutrimenthe.com), three systematic reviews evaluated the effects of nutritional interventions such as iron, folic acid or *n*-3 long-chain PUFA (LCPUFA) supplementation during pregnancy and/or in early life on the mental performance and psychomotor development of children. The objective of this review was to summarise and update current evidence, including recent data published subsequently to previous reviews. Unless stated otherwise, we searched MEDLINE and The Cochrane Database of Systematic Reviews in May 2014 for randomised controlled trials (RCT) or their meta-analyses (considered to be the best study design for answering questions about the effectiveness of an intervention). When no published RCT were available, our analysis was confined to non-RCT. However, if non-RCT are included, the results should always be interpreted with caution as potential biases, particularly selection bias, are more likely to occur. Considering that early nutrition may have important short- and long-term effects, no predefined follow-up period was specified.

Each section is followed by recent recommendations from scientific societies. Primarily, the recommendations are supported by the results of the literature searches. However, recommendations on interventions or functions not discussed in detail in the review are also presented, if considered important for clinical practice.

Iron

Iron plays a role in a plethora of processes taking place in the human body, being indispensible for energy production, oxygen transportation and DNA synthesis. Its availability is also crucial for the development of the central nervous system. Iron can be found in any structure of the brain, and it is required for myelination and neurotransmitter production. It has been well documented that iron deficiency anaemia (IDA) negatively influences brain function and impairs child development[1–3]. IDA

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Abbreviations: IDA, iron deficiency anaemia; LCPUFA, long-chain PUFA; RCT, randomised controlled trials.

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in early infancy impairs psychomotor and mental development and may have a negative influence on behaviour and psychosocial interactions. If undiagnosed and untreated for long, IDA may lead to irreversible deficits[4]. When it comes to iron deficiency without anaemia and potentially impaired development of the nervous system, a causal relationship is not clear[5,6]. Both conditions remain a common health problem in children. Data from the USA suggest that 2 % of children younger than 3 years of age may be affected by IDA, whereas iron deficiency without anaemia may be present in 12 % of this population[7].

In 2010, our group performed a systematic review (search date: December 2009) evaluating the effects of iron supplementation in non-anaemic pregnant women and non-anaemic children <3 years of age on the mental performance and psychomotor development of the children[8]. A search of MEDLINE, EMBASE and The Cochrane Library identified seven relevant RCT, five of which addressed iron supplementation in infants (0–9 months)[9–13] and two studies referred to prenatal supplementation[14,15]. None of the five RCT individually showed a beneficial effect of iron supplementation during early life on the Mental Developmental Index (MDI) of the Bayley Scales of Infant Development at different ages throughout the first 18 months. Meta-analysis of three RCT (n 561) showed that, compared with placebo, supplementation with iron had no significant effect on the children's MDI at approximately 12 months of age (weighted mean difference (WMD) 1·66; 95 % CI −0·14 to 3·47). Three of the five RCT showed a beneficial effect of iron supplementation on the Psychomotor Development Index (PDI) at some time points, whereas two did not. Meta-analysis of three RCT (n 561) showed significant improvement on the PDI at approximately 12 months of age in the iron-supplemented group compared with the control group (WMD 4·21; 95 % CI 2·31, 6·12). Two RCT showed no effect of iron supplementation on behaviour. Neither of the two RCT that addressed the influence of prenatal iron supplementation showed an effect of iron on either the intelligence quotient or the behavioural status of the children.

In May 2014, we performed an update of this systematic review, using previously used methodology, which yielded one new study by Pongcharoen *et al.*[16]. This was a follow-up study to a previously published RCT[17] in which the authors had assessed the effects of daily supplementation with iron, zinc, iron and zinc or placebo at 4–6 months on iron and zinc status and growth of children. The identified follow-up study evaluated the influence of early supplementation on cognitive performance and school performance at the age of 9 years. As many as 92 % (n 560) of the primarily included patients were available to participate in the follow-up, of which 137 received iron and 139 received placebo. The authors used the Wechsler Intelligence Scale for Children (Thai version, third edition) and Raven's Colored Progressive Matrices to assess cognitive performance, whereas school performance was assessed on the basis of school records. No statistically significant difference between the study groups regarding either cognitive performance or school performance was found.

In summary, our review showed that there is a small number of RCT addressing the impact of early iron supplementation on mental development. Existing evidence suggests that there may be a moderate positive effect of iron supplementation on the PDI score, most evident at 12 months of age. Results of identified trials indicate that there is no evidence to support an impact of iron supplementation on either the mental development or the behaviour of children. Additionally, studies evaluating prenatal iron supplementation in pregnant women also did not show any effect of iron supplementation on the mental development or the behavioural status of their children.

Recommendations from scientific societies

In 2014, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition concluded that there is no evidence that iron supplementation of pregnant women improves iron status in their offspring in a European setting. In breast-fed infants <6 months, iron supplements do not reduce IDA in populations with an already low (<5–10 %) prevalence of IDA at 6 months. There is no need for general iron supplementation of healthy European infants and toddlers of normal birth weight. Formula-fed infants up to 6 months of age should receive iron-fortified infant formula, with an iron content of 4–8 mg/l. Low birth weight infants <6 months should receive iron supplements (1–3 mg/kg per d depending on birth weight) to prevent IDA and possibly improve neurodevelopment. In populations with a high (>10 %) prevalence of IDA at 6–12 months of age, iron supplements administered from 4 to 12 months prevent IDA and may improve neurodevelopment[18].

Folic acid

Folic acid is an important micronutrient, essential for brain development and function in the pre- and early postnatal periods[19,20]. It is actively transported through the placenta, and its levels are elevated in the fetal brain during early development[21]. A deficiency of folate during pregnancy is a well-known risk factor for neural tube defects. There are a few epidemiological studies demonstrating the impact of the use of folic acid supplement by healthy pregnant women on neurodevelopment outcomes in their children, but their findings are inconsistent. Julvez *et al.*[23] showed that reported use of folic acid supplements during pregnancy was associated with improved neurodevelopment in children, whereas studies by Dobó & Czeizel[24] and Tamura *et al.*[25] did not find any association between the use of folic acid supplement during pregnancy and the women's children's neurodevelopment from 2 to 6 years of age.

In 2012, we published a systematic review (search date: December 2009) to evaluate evidence regarding whether folic acid supplementation during pregnancy and early life influences mental performance outcomes in children. Only two RCT met the inclusion criteria. Both studies involved peri-conceptional, multivitamin-containing, folic acid supplementation. Evidence from these two RCT suggested that such supplementation does not affect the postnatal mental development of infants at a mean age of 11 months, the developmental quotient at 2 years of age or the intelligence quotient and the Goodenough man drawing test quotient at 6 years of age. It was concluded that the use of multivitamin-containing folic acid supplementation during pregnancy is

associated with no benefit to the mental performance of children. These findings should be interpreted with caution because of the very limited number of studies included in this systemic review[26].

In a search up to May 2014, no new RCT were identified. In contrast, a number of observational, prospective cohort and case–control studies were identified. Several studies have shown a positive association of maternal folic acid status or folic supplement use with the mental and cognitive development of the child at different ages.

In a prospective cohort study, lower maternal erythrocytes folate and total folate intake in early pregnancy were associated with higher childhood hyperactivity and peer problem scores in the offspring[27]. In another prospective cohort study, higher maternal folate concentrations during pregnancy predicted better childhood cognitive ability[28]. In a study that used data from the 1988 National Maternal Infant Health Survey (and 1991 follow-up supplement), folic acid use was associated with improved gross-motor development with a more pronounced effect among African-American children[29]. In another prospective cohort study, higher intake of folate in early pregnancy was associated with higher scores on the Peabody Picture Vocabulary Test III (a test of receptive language that predicts overall intelligence) at the age of 3 years[30]. Roth *et al.*[31] showed in their prospective, observational study performed in a Norwegian cohort of children that maternal use of folic acid supplements in early pregnancy was associated with a reduced risk of severe language delay in children at the age of 3 years. Two studies showed an association during early childhood. In a prospective study, Chatzi *et al.*[32] found that use of high doses of supplementary folic acid in early pregnancy may be associated with enhanced vocabulary development, communicational skills and verbal comprehension at 18 months of age. Roza *et al.*[33] found that inadequate use of folic acid supplements during early pregnancy may be associated with a higher risk of behavioural problems in the offspring.

A recent case–control study from California of autism spectrum disorders (ASD) showed that maternal intake of folic acid from 3 months prior to pregnancy through the first month of pregnancy was associated with a lower risk of ASD in the offspring[34]. This observation was replicated in a Norwegian population by Surén *et al.*[35]. The potential of folic acid to prevent autistic disorders will likely generate new areas of research; however, these findings need to be confirmed in other population-based cohorts.

The limitations of the current evidence from observational trials include inadequate information on food folate and retrospective reporting of the intake of vitamins and supplements (mothers were asked to recall a period several years before the study). Moreover, some women were taking folic acid alone, whereas some were taking it in combination with iron or other micronutrients. Finally, the investigators were often unable to differentiate pre-conception supplementation from supplementation that started once the pregnancy had been detected.

Recommendations from scientific societies

The recommendations from various societies agree that all women of reproductive age should consume 0·4 mg (400 μg) of folic acid daily. The supplementation to prevent a neural tube defect (spina bifida and anencephaly) should start before pregnancy and continue for at least the first trimester[36,37].

n-3 long-chain PUFA

There has been mounting evidence showing that *n*-3 LCPUFA play an important role in brain structure and function. *n*-3 LCPUFA, particularly DHA, accumulate in all of the brain regions and retinal photoreceptors. *n*-3 LCPUFA regulate the fluidity of cell membranes as well as the activity of the ion channels, enabling synaptic transmission and providing substrate binding to membrane receptors[38]. It has been postulated that *n*-3 LCPUFA improve the cognitive process by increasing the speed of information acquisition and by accelerating visual acuity and retinal development[39].

The deposition of DHA in human brain phospholipids occurs primarily during the fetal and the early postnatal periods, continuing during the first 2 years of life[40]. Thus, sufficient provision of DHA is thought to be essential for optimal visual and neurologic development during early life. Human fetuses and young infants have limited ability to synthesise *n*-3 LCPUFA *de novo* and are supplied via maternal (placental transfer, breast milk) or external (formula) sources. Deprivation of *n*-3 LCPUFA, both prenatally and after birth, has deleterious effects on learning abilities, memory and visual grating acuity in monkeys, infants and rats[41,42].

Previously, within the NUTRIMENTHE project, we systematically evaluated the effects of *n*-3 LCPUFA supplementation in pregnant and/or lactating women on the neurodevelopment and visual functions of their children. Overall, thirteen publications – some with important methodological limitations – were included. With regard to supplementation during pregnancy, among three RCT that evaluated this intervention, one RCT (*n* 72) showed significantly better eye and hand coordination in children assessed with the Griffiths Mental Development Scales at 30 months of age. Another RCT (*n* 29) demonstrated an effect of *n*-3 LCPUFA supplementation on the cloth step of intentional solutions of the two-step problem-solving test. No other effects were demonstrated. There was no consistent effect of *n*-3 LCPUFA supplementation during pregnancy on the children's visual acuity. With regard to supplementation during lactation, among three RCT that assessed this intervention, one RCT (*n* 133) showed significant improvement of the Bayley PDI in 30-month-old children; however, there was no influence of such supplementation on the results of different tests performed either in the same group of children or in others. There was no consistent effect of *n*-3 LCPUFA supplementation during lactation on the children's visual function. Supplementation during pregnancy and lactation (three RCT) did not affect child neurodevelopment assessed up to 7 years of age. It was concluded that evidence from RCT does not demonstrate a clear and consistent benefit of *n*-3 LCPUFA supplementation during pregnancy and/or lactation on child neurodevelopment and visual acuity[43].

More recently, one systematic review[44] (search date: August 2012) assessed the effect of maternal *n*-3 LCPUFA

supplementation during pregnancy, or during pregnancy and lactation, on neurologic (IQ and motor development) and visual development (visual acuity) in the offspring. A total of twenty-three articles and abstracts involving eleven RCT, often of questionable methodological quality, were included in the review involving 5272 participants.

Compared with placebo or no intervention, the limited evidence showed that supplementation with DHA during pregnancy and lactation resulted in significantly higher cognitive scores in the subgroup of preschool children aged 2–5 years (WMD 3·92; 95 % CI 0·77, 7·08). No other statistically significant differences between groups were found in relation to cognitive or motor development in various age groups (infants, toddlers or school-aged children). Similarly, there was no effect of the intervention in pregnancy on motor development or language development. Six of the eight visual outcome assessments reported by studies found no significant differences between the supplemented and the control groups.

Subsequently to the above meta-analysis, three RCT were published. One RCT conducted in healthy infants (n 270) showed that, compared with placebo, maternal supplementation with 400 mg/d of DHA from 16 weeks' gestation until delivery significantly improved toddlers' language development at 14 and 18 months[45]. Another RCT performed in 185 infants born to mothers supplemented with 800 mg of DHA/d or a placebo from approximately 20 weeks of gestation until birth found no difference between groups in working memory and inhibitory control and on 15/16 tasks measuring attention in their 27-month-old children[46]. Finally, one RCT found that supplementation with 1·5 g/d of n-3 LCPUFA, of which 0·62 g was EPA (20 : 5n-3) and 0·79 g was DHA, during the first 4 months of lactation had no effect on processing speed, working memory, inhibitory control and socio-emotional development in their 7-year-old children[47].

Neither in our original review nor in this review did we focus on the effects of LCPUFA supplementation of infant formula. However, one meta-analysis (search date: June 2011) of twelve RCT involving 1802 infants found that LCPUFA supplementation of infant formula had no effect on infant cognition[48]. Another meta-analysis (search date: 2011) of nineteen RCT involving 1949 infants demonstrated a significant benefit of LCPUFA supplementation of infant formula on infants' visual acuity during the first year of life. More research is needed to assess the efficacy of LCPUFA supplementation on infants' visual acuity beyond 1 year of age[48,49].

Recommendations from scientific societies

Most scientific societies agree that pregnant and lactating women should aim to achieve an average daily intake of at least 200 mg of DHA. For healthy term infants, breast-feeding, which supplies pre-formed n-3 LCPUFA, is recommended. When breast-feeding is not possible, consumption of infant formula containing n-3 LCPUFA is an option. Of note, the addition of n-3 LCPUFA to infant formula is not currently mandatory, but it is permitted as an optional ingredient. The dietary n-3 LCPUFA supply should continue after the first 6 months of life, but currently there is not sufficient information for quantitative recommendations. In general, n-3 LCPUFA should be provided with ≥1 weekly portion of oily sea fish or as a DHA supplement if regular fish consumption is avoided[50,51].

Conclusions

This review focused specifically on the effects of prenatal and/or postnatal supplementation with iron, PUFA or folic acid on neurodevelopment. Even if some new data became available, the overall conclusions made previously did not change. The limited available evidence suggests that iron supplementation of infants may positively influence the psychomotor development of children, although it does not seem to alter their mental development or behaviour. The use of multivitamin-containing folic acid supplements during pregnancy did not benefit the mental performance of the offspring. Evidence from RCT did not show a clear and consistent benefit of n-3 LCPUFA supplementation during pregnancy and/or lactation on childhood cognitive and visual development. Caution is needed when interpreting current evidence, as many of the included trials had methodological limitations. These include small sample sizes, high attrition rates and no intention-to-treat analyses in many of the trials. Taken together, evidence is still inconclusive. Large, high-quality RCT to assess the effects of iron, PUFA or folic acid are still needed to further clarify the effects of these, and other nutrients, on neurodevelopment.

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H. S. initially conceptualised this study. All co-authors contributed to the initial protocol of the review. A. C. and M. R. were responsible for searching evidence on iron; D. G.-B., M. P.-L. and A. S. were responsible for searching evidence on folic acid; and P. D. and A. H. were responsible for searching evidence on n-3 fatty acids. All co-authors contributed to the preparation of the first draft of the manuscript. All co-authors contributed to (and agreed upon) the final version.

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