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Association Between Vitamin D, DHA, Folic Acid, Iodine and Zinc Supplementation During Pregnancy and Offspring Development: A Systematic Review and Meta-analysis

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ABSTRACT

Low-level status of crucial microelements in pregnant women may expose the offspring to suboptimal conditions during fundamental phases of fetal development, and it may have long-term effects on their health outcomes. The review summarizes the relationship between vitamins: DHA, folic acid, iodine and zinc intake during pregnancy and their role in maternal and fetal development; also introduces findings from clinical trials that evaluated the association of these supplements deficiency with outcomes in the fetus and neonate. The aim was to find the potential benefits of prenatal vitamin usage containing these compounds and risks for the mother and fetal development as a consequence of deficiency. We have focused on vitamin D, its influence on bone mineralization, prevention of rickets and other non-skeletal outcomes. We examined DHA functions (including the importance of n3 PUFAs in cognitive functions) and its association with decreased risk of preterm birth, preeclampsia, IUGR and GDM. Also, we raised the issue of l-methylfolate, as a prevention of neural tube defects, other pregnancy-related complications, and folic acid-related gene mutation in the MTHFR. We investigated iodine supplementation, its relationship to cretinism prevention, and its cost-effectiveness relative to no supplementation among pregnant women in a mildly iodine-deficient population. We discussed the validity of additional zinc intake and its influence on fetal growth, weight, and gestational age. Results indicate an advantageous effect of supplementation on maternal and fetal outcomes. Appropriate supplementation brings notable benefits. However, it is important to avoid exceeding the recommended doses, as it may have the opposite effect.

Keywords: Supplementation, Pregnancy, Vitamin deficiency, Offspring outcomes, Fetal development

1. INTRODUCTION

Vitamin D

Vitamin D is a critical mediator in maintaining bone health and is essential in bone mineralization. Its main functions are calcium absorption and metabolism. Vitamin

D is mostly synthesized cutaneously through sunlight exposure; it can also be acquired through diet in fatty fish, eggs, liver, fortified products, such as cereals and dairy alternatives. Vitamin D deficiency during pregnancy may disrupt the development of offspring during crucial phases and have long-term effects on fetal health outcomes. Maternal deficiency may result in abnormal bone development and growth in newborns or the risk of rickets in children, and contribute to dilated cardiomyopathy and seizures caused by hypocalcemia. Other nonclassic actions that may affect various aspects, such as non-skeletal health outcomes and longer-term problems, include schizophrenia and type 1 diabetes. Research into the impact of vitamin D remains inconclusive. In a 2 double-blind randomized trial with 240 pregnant women, who received 10 or 20 μg vitamin D3/d (evaluated by BMI) from 12 GW until delivery, the authors found an association between vitamin D, maternal BMI and offspring outcomes (Alhomaid et al., 2021).

The WHO guidelines suggest that pregnant women maintain a supplemental dose of 2000 IU of vitamin D daily. For pregnant women with risk factors such as obesity and metabolic disorders, the dosage can be increased, as supported by a randomized trial showing that supplementation with 800 IU per day can maintain maternal and fetal serum levels at sufficient levels (Alhomaid et al., 2021).

Docosahexaenoic acid (DHA)

Docosahexaenoic acid (DHA) is instrumental in the nervous system and cognitive ability. It contains N-3 long-chain polyunsaturated fatty acids (n-3 PUFAs), which are important in brain function, neuronal membrane structure, and the development of the myelin sheath and retina. The majority of n-3 PUFAs in the brain are DHA, underscoring DHA's importance in maintaining brain function. DHA is naturally concentrated in oily fish such as sardines, salmon, mackerel, tuna, and herring, as well as in other seafood. It can also be acquired in fortified foods like milk and yogurt, eggs, and algal oil. The fetus and placenta possess limited capacity for de novo DHA synthesis. There are cases where pregnancy complications, low maternal DHA levels, or placental fatty acid dysfunction in transport lead to DHA deficiency in the offspring, which may lead to long-term neurological disorders. A case–control study measured the amount of DHA + EPA in total fatty acids. In recent years, studies demonstrated the neuroprotective potential of DHA in the management of Alzheimer's disease (Patrick, 2019), breast cancer (Fabian et al., 2015), cardiac failure, and ADHD. The recommended dosage is 300 mg daily in the first trimester, increasing to 600 mg throughout the second and third trimesters.

Folic acid

Folic acid (vitamin B9) is a necessary nutrient required for DNA replication and as a substrate for multiple enzymatic reactions, which are involved in vitamin metabolism and amino acid synthesis. Periconceptional folic acid supplementation is essential in reducing the risk of neural tube defects. Nutritional deficiency is frequently identified as a contributing factor to maternal disorders (anemia, peripheral neuropathy) and fetuses (congenital abnormalities). The primary clinical objective is to prevent spina bifida by supporting the structural development of the fetal neuraxis. This relationship has been analyzed in three observational studies and four publications, all of which found a clear link between folic acid supplementation and a lower risk of neural tube defects (n= 990372). Unlike other prenatal supplements, folic acid is unique because the most critical window for its use is actually before conception.

Researchers in the Japanese cohort (n = 92269) compared pregnancy outcomes between women who achieved optimal pre-conceptional folic acid intake and those with delayed or insufficient supplementation (Nishigori et al., 2019). Folate requirements increase during pregnancy because it is also necessary for the growth and development of the fetus.

Furthermore, a common folic acid-related mutation in the MTHFR (methylenetetrahydrofolate reductase) gene is often present. It affects the ability of folic acid to transform into the active form, L-methylfolate. Pregnant women with these mutations, instead of regular folic acid, should supplement active folate or consume foods with folate in naturally occurring sources (Greenberg et al., 2011). Foods rich in folate include cereals and breads, leafy green vegetables (especially spinach and broccoli), citrus fruits, nuts, and legumes. The daily recommended dosage is 400 mcg at least 3 months before pregnancy begins and 400-800mcg during the first 12 weeks of pregnancy. Other studies recommend continuing folic acid throughout pregnancy, especially if anemia develops. For individuals with a higher risk of NTDs, a therapeutic daily dose of 5 mg of folic acid may be advised.

Iodine

Iodine is a key substrate for the synthesis of thyroid hormones, which are crucial in neurogenesis and fetal brain architecture. Iodine demands for women increase significantly during pregnancy to ensure a proper supply to the fetus. Foods rich in iodine include seafood, seaweed, fish, dairy products, eggs, and iodized salt. Oral iodine supplementation is associated with infant survival and

reduced risk of cretinism. The thyroid hormone is crucial in proper neuronal migration and myelination of the nervous system during fetal and postnatal life. Hypothyroxinemia in these crucial periods may cause brain damage, neurological abnormalities and intellectual disability. Studies demonstrated that mild iodine deficiency during pregnancy is a risk factor for permanent brain damage and cognitive dysfunction in infants (Monahan et al., 2015). 11 trials involving over 2700 women contributed data for the comparisons of iodine supplementation and maternal primary outcomes, such as postpartum hyperthyroidism (Harding et al., 2017).

The Universal Salt Iodization program has significantly contributed to decreasing iodine deficiency in the population. Still, iodine deficiency remains in several geographic regions. The WHO (2016) and UNICEF established recommended iodine intakes of 150–290 μg per day. Results of randomized controlled trials currently underway in areas with mild to moderate iodine deficiency should help clarify the issue.

Zinc

Zinc is crucial for numerous biological processes, including cellular division, protein synthesis, and nucleic acid metabolism. Mild to severe zinc deficiency is relatively rare in human populations; moderate depletion appears to be quite prevalent. Inadequate zinc levels during gestation have been linked to reduced birth weight, fetal loss, congenital malformations, IUGR (intrauterine growth retardation), preterm or post-term deliveries, and prolonged labour (Carducci et al., 2021). Children with zinc deficiency are at increased risk of restricted growth, respiratory tract infections, and developing diarrhoeal diseases (WHO, 2011).

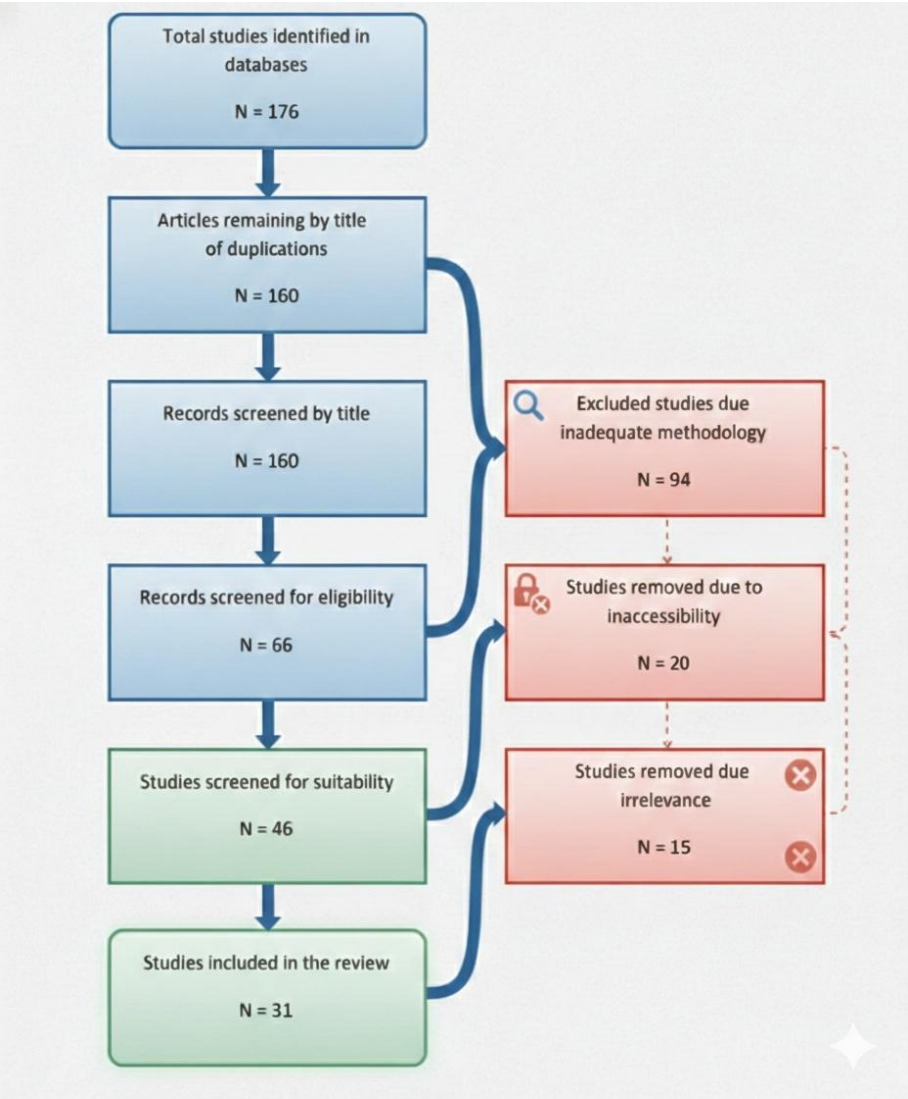

Figure 1. PRISMA flow diagram representing study selection process (N - number of articles)

2. REVIEW METHODS

Literature review was conducted in medical databases as PubMed, UpToDate and relevant subject literature published in the last 30 years. We manually searched the references to identify additional RCTs, using the terms "supplementation in pregnancy", "folic acid", "vitamin D", "iodine", "vitamin deficiency", or "vitamins in pregnancy".

3. RESULTS & DISCUSSION

Vitamin D

Women taking vitamin D supplements exhibited significantly higher serum 25(OH)D concentrations. Nevertheless, vitamin D deficiency persisted despite exogenous intake. Vitamin D supplementation during pregnancy was associated with a reduced risk of small-for-gestational-age (SGA) infants, without an increased risk of fetal or neonatal mortality or congenital malformations (Bi et al., 2021). Neonates who received prenatal vitamin D supplementation had higher calcium levels, significantly greater birth weight and height, greater neonatal femur length and skinfold thickness, and higher Apgar scores. In women with low serum (<50 nmol/L) levels, supplementation of 20 μg (800 IU) provided significant benefits; maternal and cord 25(OH)D levels increased to ≥50 nmol/L. Present protocols may be inadequate for women with obesity, who face an increased risk of persistent deficiency throughout pregnancy. It may result in infants born with deficient 25(OH)D concentrations (Alhomaid et al., 2021).

Vitamin D supplementation showed no association with infants' outcomes of upper respiratory tract infections, asthma, eczema, or the presence of allergy-specific immunoglobulin E.

Docosahexaenoic acid (DHA)

In patients with preeclampsia, DHA concentrations were significantly reduced. On top of it, women with the lowest n-3 PUFA concentrations were more prone to suffer from preeclampsia than those with the highest levels (Irwinda et al., 2021). Decrease in DHA in these patients was already present at 16–20 weeks of gestation. These results suggest that early maternal DHA levels may predict preeclampsia. Researchers measured DHA levels in cord blood from GDM women and compared them with those of pregnant women with normal blood glucose levels. Despite unchanged or increased maternal DHA levels, DHA levels in cord blood were decreased in GDM cases (Cardoso et al., 2018). These results suggest that in pregnancies complicated by diabetes, the placental capacity for transporting n-3 PUFAs, specifically DHA, is significantly compromised. To summarize, higher doses of DHA intake do not seem to prevent GDM; however, women with gestational diabetes mellitus during pregnancy may benefit from supplements with DHA.

To assess nutritional risk factors, the proportions of DHA and EPA were measured in the preterm birth group and compared with a gestationally age-matched or full-term cohort. Women with preterm birth had lower plasma DHA levels (Jiang et al., 2023). It suggests insufficiency of DHA and EPA during pregnancy may be a highly correlated risk factor for preterm birth.

Also, the decrease in maternal DHA levels is a cause or consequence of Intrauterine growth retardation (IUGR). Further study of this disease led to the conclusion that DHA insufficiency may contribute to microcephaly. Docosahexaenoic acid supplementation during pregnancy may protect against small head circumference and fetal microcephaly (Cardoso et al., 2018). DHA supplementation also appears to reduce the risk of depression during pregnancy. In clinical trials, researchers evaluated the effects of DHA on brain morphology and mental function in patients with Alzheimer's disease (Patrick, 2019). Consuming DHA in phospholipid form may be better transported across the BBB. Other meta-analyses examining marine omega-3 intake reported a positive association with reduced breast cancer risk. Use of DHA supplements in women aged more than 50 years was associated with a 32% reduction in risk of breast cancer (Fabian et al., 2015).

Folic acid

Fortification of grain products with folic acid has been mandatory since 1998, and the legislative mandates were associated with a significant increase in erythrocyte folate concentration among women of reproductive age and a decrease in the prevalence of infants born with NTDs. However, a recent study reported that the usual intake of folic acid from mandatory fortification is ~115 μg per day, suggesting a continued need for supplementation.

Newer findings indicate that there is still room for improvement in the uptake of periconceptional folic acid supplementation. Furthermore, in the population, some mutations have been detected that are associated with lower folate concentrations and a higher risk of NTDs than in the absence of these polymorphisms. MTHFR is involved in folate metabolism and the transfer of methyl groups used in the synthesis of nucleotides and other substrates, including the conversion of homocysteine to methionine. Due to the high

prevalence of MTHFR polymorphisms and their impact on enzymatic activity, current research favours L-methylfolate over folic acid to more effectively prevent folate-related pathologies (Greenberg et al., 2011). In a double-blind, randomized, placebo-controlled trial of women of childbearing age, findings show that L-methylfolate increases red blood cell folate concentrations more effectively than folic acid. Active form supplementation may be particularly important for individuals with these types, given their genetic predispositions.

In active erythropoiesis, which requires adequate supplies of three key nutrients: folate, cobalamin (vitamin B12), and iron, in settings of low folate and/or vitamin B12, anemia will likely ensue. A recent retrospective analysis of anemia in pregnancy compared two groups of pregnant women: those who were prescribed prenatal medical food, in addition to 0.4 mg of folic acid and vitamin B12, and those who were prescribed standard prenatal vitamins containing only 0.8 to 1.0 mg of folic acid. The women in the high-folate, high-dose vitamin B12 group demonstrated significantly higher hemoglobin levels at delivery (11.8 g/dL vs 10.7 g/dL; P = .001) than those in the control standard prenatal vitamin group (Williams et al., 2011). Indirect evidence suggests that folate may be important in the timing of labour. Observational studies link a shorter duration of pregnancy to lower serum folate levels and to a lack of folic acid supplementation. Studies suggest that folic acid supplementation alone may protect against Premature birth (PTB), without increasing the risk of miscarriage, structural anomalies, multiple pregnancy, or stillbirth. Women using preconceptional folate supplementation compared with non-users had a significant reduction in spontaneous PTB. Beyond preventing NTDs and preterm birth (PTB), periconceptional folic acid supplementation protects against other congenital anomalies, such as congenital heart disease and oral clefts. The specific mechanism is not known, but folic acid may prevent structural anomalies in the fetus by regulating homocysteine metabolism.

Iodine

Iodine insufficiency during pregnancy can cause maternal and fetal hypothyroidism and impairment of fetal neurological development. The consequences depend upon the severity and timing of the deficits. The most severe manifestation is cretinism. The systematic review of 1,361 articles identified eight studies that investigated the association between IQ and iodine concentration. Providing pregnant women with iodine supplements resulted in an IQ increase of 1.22 points per child. These results remained consistent and robust throughout testing (Monahan et al., 2015). The majority of the evidence derives from settings with mild or moderate iodine deficiency and may therefore not be suitable for settings with severe deficiency. In moderate-to-severely iodine-deficient regions, controlled studies and clinical observations show that iodine supplementation initiated prior to or during early gestation reduces the incidence of cretinism, increases birthweight (without exceeding the norm), reduces perinatal and neonatal mortality rates and generally improves developmental outcomes in children by 10–20%. Meta-analyses estimate that iodine-deficient populations undergo a mean reduction in IQ of 12–13.5 points. Data from 543 participants show that while iodine supplementation lowered the likelihood of postpartum hyperthyroidism by 68% (average RR 0.32), it also resulted in a 15-fold increase (average RR 15.33) in digestive intolerance among pregnant women (Harding et al., 2017).

In infants and children compared with those who did not receive iodine, primary outcomes among those who received iodine supplements included a 34% lower likelihood of perinatal mortality; this difference was not statistically significant. In areas of chronic severe iodine deficiency, fetal and maternal hypothyroxinemia can occur from early gestation onward. Depending on access to iodized salt in particular regions, iodine supplementation may be necessary to ensure pregnant women receive adequate iodine intake. In nearly all areas affected by iodine deficiency, salt iodization is the most cost-effective way to deliver iodine and improve maternal health and infant development (Monahan et al., 2017).

The US Institute of Medicine established a recommended dietary allowance of 150-220 μg a day for women during pregnancy and 290 μg a day while breastfeeding. However, offspring of mothers with excessive iodine intake face a higher risk of congenital hypothyroidism.

Zinc

Using a model comparing reported zinc intake to recommended levels, researchers found that the majority of participants had inadequate zinc intakes. Most studies estimated the effects of zinc against a background of other micronutrient supplements. In 25 randomized controlled trials involving over 18,000 women and infants, researchers compared the effects of prenatal supplementation to a non-user control group. The evidence suggests zinc supplementation reduces the incidence of preterm birth (RR 0.87, 95% CI 0.74 to 1.03), stillbirth (RR 1.22, 95% CI 0.80 to 1.88) and low birthweight (RR 0.94, 95% CI 0.79 to 1.13) (Carducci et al., 2021). Other researchers

analyzed data from 16 trials—encompassing 7,818 births and 960 preterm cases—and found that zinc supplementation reduces the risk of preterm birth (RR 0.86 [95% CI 0.75, 0.99]) (Chaffee et al., 2012).

A meta-analysis showed that maternal zinc supplementation is beneficial, leading to a small but significant reduction in preterm birth. There was no specific evidence proving that supplemental zinc affected any parameter of fetal growth. Few findings reached statistical significance, as trial results often showed minimal differences between the zinc-supplemented and control groups. Overall, sources showed that only the risk of preterm birth reached statistical significance. Additionally, there appeared to be a trend toward decreased diarrhea at 6–13 months of age with prenatal zinc (Carducci et al., 2021). Across all trials, the most consistently favourable and reasonable zinc supplementation outcome was an increase in maternal serum zinc status in late gestation (Table 1).

Table 1. comparison of supplement dosage and positive results/prevented disease

Supplement name	Reference study	Recommended dosage for supplementation	positive results, decreased risk of any disease occurrence
Folic acid	Greenberg et al., (2011)	400-800 mcg daily for all other reproductive-aged women.	minimized risk of NTDs in offspring,
	Williams et al., (2011)		prevent anemia and decrease the risk of premature birth, oral clefts and congenital heart defects
	Nishigori et al., (2019)		no association
Docosahexaenoic acid (DHA)	Jiang et al., (2023), Cardoso et al.. (2018), Irwinda et al., (2021),	300 mg per day in the first trimester, 600 mg in the second and third trimester	minimized the risk of preeclampsia, preterm birth, IUGR, gestational diabetes mellitus and postpartum depression
Vitamin D	Bi et al., (2018)	2000 IU of vit. D daily	greater birth weight and greater height, greater neonatal femur length and skinfold thickness, higher Apgar scores.
	Alhomaid et al., (2021)	800 IU	higher concentrations of25(OH)D in maternal and umbilical cord
Iodine	Zimmermann et al., (2012)	150 μg to 290 μg a day	for cretinism prevention
	Monahan et al., (2015), Ian Darnton-Hill, 2017		higher IQ
	Harding et al., (2017)		decreases the likelihood of postpartum hyperthyroidism.
Zinc	Carducci et al., (2021)	studies have not shown a specific dosage of supplementation	reduced birth weight prevention, congenital malformations,

	Chaffee et al., (2012)	5 mg to 50 mg zinc a day	intrauterine growth retardation, prolonged labour and preterm or post-term deliveries.

4. CONCLUSION

Results show an advantageous effect of supplementation with vitamin D, DHA, Folic Acid, iodine, and zinc on maternal and fetal outcomes. Recommended Vit. D supplementation set as 2000 IU/d during pregnancy is associated with improved infant growth, reduced risk of SGA and does not increase the risk of fetal or neonatal mortality or congenital abnormalities. Studies showed that a daily intake of 200-600mg of DHA in healthy pregnant women has positive long-term results. Supplementation improves the pregnancy period by minimizing the risk of diseases such as preterm labour, preeclampsia, GDM, IUGR, and postpartum depression. Also, it counteracts DHA insufficiency in infants by increasing maternal DHA levels, improving fatty acid transport across the placenta, and preventing long-term developmental disorders of the nervous system caused by some pregnancy complications. Prenatal DHA may increase infants' attention and state regulation. Dietary supplementation with an active folate of 400–800 mcg during the periconceptional period reduces the risk of NTDs in offspring and prevents anemia (by increasing maternal RBC production); it also decreases the likelihood of congenital heart defects and oral clefts. Some trials have found no association between the incidence of NTDs and preconceptional folic acid supplements. The most severe manifestation of utero iodine deficiency is cretinism, associated with cognitive impairments, motor spasticity, squint and deaf mutism.

The available evidence suggests that a daily intake of 150-220 μg of iodine reduces the risk of postpartum hyperthyroidism and cretinism; it also results in higher IQ, but possible adverse effects include digestive intolerance during pregnancy. Researchers estimated a correlation between poor maternal zinc status and reduced birth weight and height in offspring. Results did not show an unequivocal effect of zinc supplementation during pregnancy. In specific populations, zinc supplementation increases both mean gestational age and birth length. Targeted zinc supplementation improves clinical outcomes for individuals identified as zinc-deficient. Current evidence does not support exceeding the doses specified in this review, as higher intakes do not confer additional therapeutic benefit.

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Informed consent

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Ethical approval

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Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on a reasonable request to the corresponding author.

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