# DOCOSAHEXAENOIC ACID AND ITS PRINCIPLE ROLES DURING PREGNANCY

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**Docosahexaenoic acid (DHA) is an important dietary component, yet there is a general tendency for it to be under-consumed during pregnancy. This is particularly concerning given the growing evidence base that links DHA to fetal development. This article reviews current DHA pregnancy intakes, guidelines and the evidence base focusing on DHA's role in fetal/infant brain and eye development.**

Docosahexaenoic acid (DHA) is an Omega-3 (n-3) polyunsaturated fatty acid that cannot be produced efficiently by the body, yet is essential to life. Subsequently, it is needed from other sources, namely fish and fish-oil products.[1] Metabolically, DHA can be produced by the body (Figure 1), but only in very small amounts with isotope studies suggesting that its conversion from the parent fatty acid alpha-linolenic acid (ALA) into eicosapentaenoic acid (EPA) and then DHA is no more than 5.0% and probably no more than 1.0% amongst adults following Western diets.[2]

As shown in Figure 1, the Omega-6 (n-6) and n-3 acids share the same metabolic pathway and use of the same enzymes. Subsequently, higher dietary intakes of n-6 fatty acids skew the metabolic pathway in the direction of forming more arachidonic acid and away from the synthesis of EPA and DHA.[3]

While our ancestors once followed a diet providing a balanced 1/1 ratio of n-6: n-3 fatty acids, this has changed over time. In modern times, increased consumption of vegetable oils has now resulted in a 20-25/1 ratio of these fatty acids, with subsequent reductions in DHA production by the body; a process that is already limited.[3,4]

Dietary sources of n-3 fatty acids (per 100g of food eaten) include walnuts (7.5g), mackerel (5.6g), kippers (3.4g), herring (1.8g), sea bass (1.7g), chicken (1.4g), almonds (0.3g), eggs (0.1g).[5] Looking at these figures, it can be seen that the n-3 polyunsaturated fatty acid content of foods is highly variable, although oily fish is a particularly good source. Unfortunately, during pregnancy, there is a general tendency for mothers to avoid eating oily fish, with concerns about mercury and other contaminants contributing to this.[6] A dislike for the taste of fish may further contribute to low fish intakes and inadequate intakes of the n-3 fatty acid DHA.

## RECOMMENDATIONS

The European Food Safety Authority (EFSA) has set an adequate intake (AI) target of 250mg of EPA plus DHA for adults. Further to this, an additional 100-200mg DHA has been advised for pregnancy and lactation to compensate for maternal dietary oxidative losses of DHA and to account for growing stores needed by the foetus/infant.[7]

Work by Koletzko and colleagues forms the basis of the International Society for the Study of Fatty Acids and Lipids (ISFAAL) statements and recommendations.[8] These guidelines have been published in two scientific journals which advise that pregnant and lactating women should obtain at least 200mg per day of DHA from dietary sources,[9,10] although up to 1.0g per day DHA has been used safely in randomised clinical trials.[9]

Considering the dietary intakes and conditions of Asian populations, a systematic review of 78 randomised controlled trials concluded that pregnant Asian women should achieve an extra ≥200mg DHA per day, ideally striving for

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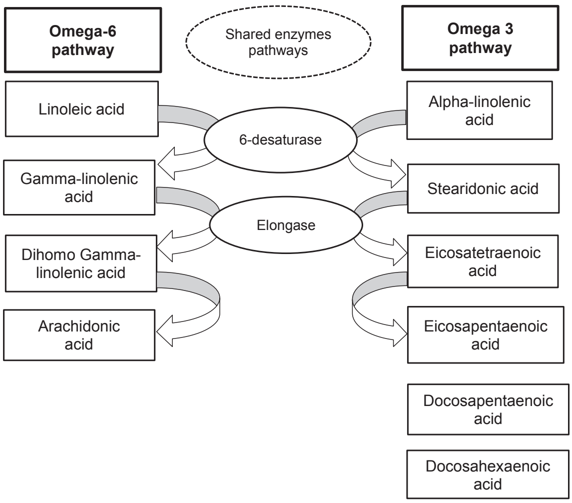
Figure 1: Metabolic endogenous production of DHA




Source: Adapted from Ruxton et al[3]

a total intake ≥300mg DHA per day. The review also concluded that higher intakes of 600-800mg DHA per day could provide greater protection against early preterm births in this population group.[11]

## DHA INTAKES

As shown in Table 2, a number of studies have measured DHA intakes in pregnancy. European research highlights variations in DHA intakes, with Spanish women tending to have some of the highest and German mothers some of the lowest median daily DHA intakes.[12] Interestingly, 43% of women took dietary supplements in week 20 and 39% in week 30 of pregnancy, with multivitamin use being most common.[12]

The Canadian Alberta Pregnancy Outcomes and Nutrition (APrON) cohort measured DHA intakes during each trimester of pregnancy and after birth. Researchers found that only 27% of women during pregnancy and 25% of mothers three months after birth met European Union DHA recommendations.[13] Earlier Canadian work reported even lower mean DHA intakes: 160mg per day derived from food frequency questionnaire data collected during weeks 28 and 35 of pregnancy.[14]

In Mexico, median DHA intakes amongst women (aged 18-35 years) interviewed 18-22 weeks into their pregnancies were 55mg per day. While eggs, chicken and fresh and canned fish were the main contributors to DHA intakes, these were more likely to be eaten by women who had completed high school. It was also concluded that the high n-6:n-3 ratio of the diets of these women was likely to over-ride any possible n-3 benefits.[15]

Work conducted in China showed that DHA intakes during pregnancy vary geographically. Those living in coastal regions (n=42) had higher DHA intakes (93.9mg per day) compared with those living inland (n=40) who had intakes of

Table 1: DHA recommendations for pregnancy

| Reference | Country | DHA |
|---|---|---|
| EFSA (2010)7 | European focus | **Total intake 350-450mg DHA/day**<br>250mg/day EPA+DHA and an extra 100-200mg/day preformed DHA during pregnancy and lactation. |
| Koletzko et al (2007)[9] | European focus | **Total intake ≥200mg DHA/day**<br>Pregnant and lactating women should aim to achieve dietary intakes of 200mg DHA/day. Intakes of up to 1.0g/d DHA or 2.7g/day n-3 long-chain PUFA have been used in RCTs without significant adverse effects. |
| Koletzko et al (2008)[10] | European focus | **Total intake ≥200mg DHA/day**<br>Pregnant and lactating women should aim to achieve an average intake of at least 200mg/day DHA. |
| Koletzko et al (2014)[11] | Asian perspectives | **Total intake ≥200mg DHA/day**<br>Additional supply ≥200mg DHA/day, usually achieving a total intake ≥300mg DHA/day. |

Key: EFSA, European Food Safety Authority; DHA, docosahexaenoic acid.

Table 2: DHA intakes in pregnancy

| Study & Country | Methods | DHA intakes | Main findings |
|---|---|---|---|
| Franke et al (2008)[12] Europe | FFQ in weeks 20 & 30 of pregnancy (n=62) | 155mg/1000kcal wk20 - Spain<br>161mg/1000kcal wk30 - Spain<br>119mg/1000kcal wk20 - Germany<br>124mg/1000kcal wk30 - Germany<br>122mg/1000kcal wk20 - Hungary<br>125mg/1000kcal wk30 - Hungary | DHA intakes varied across the European cohorts. |
| Jia et al (2015)[13] Canada | 24-hour dietary recalls used in the APrON cohort (n=600) | 159mg/d - 1st trimester<br>187mg/d - 2nd trimester<br>237mg/d - 3rd trimester<br>186mg/d - Postpartum | Only 27% women during pregnancy and 25% women met the EU DHA recommendation. |
| Innis et al (2003)[14] Canada | FFQ at weeks 28 and 35 of pregnancy (n=55) | 160mg/d (range: 24 to 524mg/d) | DHA intakes were low amongst pregnant women which could have functional significance. |
| Parra-Cabrera et al (2011)[15] Mexico | Retrospective FFQ at weeks 18-22 pregnancy from the previous 3 months (n=1364) | 55mg/d and an omega 6:3 ratio of 12:1 | DHA intakes were lower than recommended values. |
| Zhang et al (2013)[16] China | DHA intakes measured amongst different geographical regions (n=123) | 93.9mg/d in the coastal group<br>41.8mg/d in the river/lake group<br>41.1mg/d in the inland group | DHA intake ranged between geographical regions. |
| Dwarkanath et al (2009)[17] South India | FFQ measuring DHA in all three trimesters (n=829) | 11mg/d (median intake) | Dietary interventions are needed to improve DHA intakes. |
| Zhao et al (2013)[18] Canada | FFQ at weeks 24-28 of pregnancy (n=307) | 100mg/ d (median intake) | More than 90% of women had DHA intake <300mg/d. |

Key: APrON, Alberta Pregnancy Outcomes and Nutrition cohort; DHA, docosahexaenoic acid; EU, European Union; FFQ, food frequency questionnaire.

just 41mg per day.[16] Equally, work carried out in South India during pregnancy (n=829) showed that DHA intakes increased with each trimester, with median intakes being particularly low at 11mg per day.[17]

Zhao and colleagues (2013) assessed the alterations in plasma fatty acid concentrations during the third trimester of pregnancy and the effects of food intakes at 24-28 weeks gestation.[18] The median intake of DHA was only ~100mg per day, although dietary intakes of DHA were positively and significantly associated with plasma DHA levels. Plasma DHA levels decreased significantly from weeks 24-28 to 32-35, suggesting maternal DHA depletion in the third trimester of pregnancy in this Canadian cohort.[18]

At this point, it should also be considered that while continued research is needed to determine DHA intakes in pregnancy, suitable biomarkers should also be used alongside dietary assessment tools. For example, DHA levels present in plasma, cell membranes and adipose tissue would all add to the comprehensiveness of future investigations.[19]

## ROLE(S) OF DHA IN PREGNANCY

n-3 fatty acids are important during pregnancy as these are transferred through the placental

Table 3: RCTs focusing on brain development

| Study & Country | Methods | Findings |
|---|---|---|
| Jensen et al (2010)[23] US | RCT from delivery until four months after birth (n=119). Women received 200mg/d DHA algal oil or a vegetable oil. Cognitive and visual tests at five years of age. | Infants receiving DHA performed significantly better on sustained attention tasks (p<0.008). |
| Jensen et al (2005)[24] US | RCT from delivery until four months after birth (n=227). Women received 200mg/d DHA algal oil or a vegetable oil. Infant tests up to 30 months of age. | DHA supplementation was found to improve the Bayley Psychomotor Development Index at 30 months of age (p<0.01). |
| Judge et al (2007)[25] US | DB PC RCT (n=29). Ate a functional food containing 300mg DHA per bar (five bars per week) or placebo from 24 weeks pregnancy until delivery. Infant cognitive tests at nine months. | DHA bar ingestion significantly improved performance of problem-solving tasks (p=0.017), but not memory recognition. |
| Helland et al (2003)[26] Norway | DB RCT (n=341). Women took cod liver oil containing 803mg/10mL DHA from week 18 pregnancy until delivery, or a corn oil placebo. Infant cognitive tests at six and nine months. | Children born to mothers taking cod liver oil had higher mental processing scores. Children's IQ scores at age four years also correlated positively with maternal DHA intake. |
| Van Goor et al (2011)[27] Netherlands | DB PC RCT (n=114). Women took: 1) 220mg/d DHA, 2) 220mg/d DHA+AA or 3) placebo from 14-20 weeks pregnancy until delivery. Neurodevelopment tests at 18 months. | Children with minor neurological dysfunction had lower umbilical venous DHA. Short-term DHA supplementation did not improve any other neurodevelopment outcomes. |
| Gould et al (2014)[28] Australia | RCT (n=185) infants born to mothers who took 800mg/d DHA or placebo from 20 weeks pregnancy until after birth. | Maternal supplementation was not found to improve attention or the working memory of offspring. |

Key: AA, Arachidonic acid; DB, double-blind; DHA, docosahexaenoic acid; IQ, Intelligence Quotient; RCT, randomised controlled trial.

and milk supply, subsequently impacting on fetal/infant brain and visual function.[20] DHA also has unique structural properties which provide optimal conditions for cell membrane functions, which includes the grey matter of the brain and visual pathways.[21]

Given this, DHA is important for normal brain and retinal tissue development tissues (especially myelin and retinal photoreceptors). It is also needed for normal neurotransmission and connectivity.[6] In fact, DHA found in the nervous tissue and retina contributes to over 90% of all n-3 fatty acids.[22]

The next section of this article evaluates evidence from RCTs focusing on the role of DHA supplementation during pregnancy and lactation in relation to brain and eye development.

## BRAIN DEVELOPMENT

Due to the rapid growth of nervous tissue, both foetuses and newborns have high DHA requirements. Studies measuring DHA concentrations in the brain show a continuously increasing uptake of DHA - starting from the 22nd week of pregnancy through to the early years of a child's life.[22]

A PubMed search identified six RCTs studying the effects of DHA supplementation on brain development. Four of these studies reported positive findings, with most interventions taking place in the third trimester, running into or after delivery (Table 3).

Jensen and colleagues undertook two trials. DHA derived from algal oil (200mg per day) was associated with infants performing significantly better on sustained attention tasks[23] and Bayley Psychomotor Development Index (a measure of infant development)[24] when taken from delivery for four months after birth.

Other work used either functional foods providing DHA (300mg per bar), or cod liver oil containing DHA (803mg per 10ml). The ingestion of five functional bars per week from

Table 4: RCTs focusing on eye development

| Study and country | Methods | Findings |
|---|---|---|
| Dunstan et al (2008)[29] Australia | DB PC RCT(n=98) pregnant women received 2.2g DHA, 1.1g EPA or olive oil from 20 weeks gestation until delivery. | Children in the fish oil-supplemented attained a higher score for eye and hand coordination score than the placebo group (p=0.021). |
| Judge et al (2007b)[30] US | DB PC RCT (n=30). Ate a functional food containing 300mg DHA per bar (five bars per week) or placebo from 24 weeks pregnancy until delivery. Visual tests on infants at four and six months. | DHA supplementation significantly improved infant visual acuity at four months (p=0.018). |
| Malcolm et al (2003)[31] UK | RCT (n=100) pregnant women received fish oil or an oleic acid placebo supplement from 15 weeks until delivery. Infant retinal development assessed during the first week of life. | Infants in the highest quartile for cord blood DHA had higher retinal sensitivity compared with infants in the lowest quartile. |
| Dunstan et al (2007)[32] Australia | DB PC RCT (n=98) pregnant women received 2.2g DHA, 1.1g EPA or olive oil from 20 weeks gestation until delivery. | DHA in breast milk correlated positively with Griffith's developmental scores including hand and eye coordination. |
| Birch et al (2010)[33] US | DB RCT (n=343). Term formula-fed infants received one of four infant formulas containing different amounts of DHA. | Infants fed the control formula (no DHA) had significantly poorer visual acuity (p<0.001). DHA supplied at 0.32% total fatty acids improved visual acuity. |

Key: DB, double-blind; DHA, docosahexaenoic acid; PC, Placebo Controlled; RCT, randomised controlled trial.

the third trimester significantly improved infants' performance of problem-solving tasks at nine months of age.[25] Equally, Helland et al found that children born to mothers taking cod liver oil from 18 weeks into their pregnancies had higher mental processing and IQ scores.[26]

Two studies found limited effects of DHA supplementation, possibly due to low study compliance.[27,28] Supplement compliance data from a subset of the DHA for Maternal and Infant Outcomes (DOMInO) trial[28] showed that this was 47.5% at follow-up, indicating that this could have contributed to the shortfall in findings.

## EYE DEVELOPMENT

Five RCTs identified through PubMed looked at the effects of DHA on visual/eye development (Table 4). All studies reported benefits, although differing timescales and doses were used. Three studies found that DHA taken from mid-pregnancy until delivery helped to improve hand and eye co-ordination,[29] infant visual acuity[30] and retinal sensitivity.[31]

Dunstan and colleagues[32] found that infant DHA status at one year of age was related to maternal DHA levels during pregnancy and six months after birth, but not antenatal supplementation, indicating the importance of continuing this after birth. Birch and authors[33] focused on the composition of infant formulas, finding that DHA supplied at a level of 0.32% of total fatty acids was most effective at supporting visual acuity.

## DISCUSSION

There is a growing body of evidence supporting the importance of DHA in pregnancy. Unfortunately, habitual intakes are substantially lower than European targets set at 250mg per day EPA+DHA for adults, with an additional 100-200mg per day preformed DHA recommended during pregnancy and lactation.[7]

Further to this, the area in which a women lives and her level of education can also affect how much DHA is consumed from dietary sources,[15,16] while other lifestyle factors, such as alcohol intake, have also been found to reduce maternal DHA plasma concentrations.[34]

While educational interventions have shown some improvements in pregnancy fish and DHA consumption, mean intakes still fall short of

*Given that the mother is the main provider of a child's DHA when in utero and breastfeeding, it is important for health professionals to be aware of DHA pregnancy guidelines.*

guidelines. For example, Oken and authors[35] found that DHA intakes were just 70mg per day in the fish advice group and 161mg/day in the advice and grocery store gift card group who used these to buy fish with a low mercury content. Expectant mothers were guided about which fish to buy, using a booklet which listed fish according to their DHA content.

Subsequently, alternative approaches are needed, with supplementation programmes being one way forward. Interestingly, findings from the APrON study showed that pregnant and breastfeeding women taking a supplement were 10.6 and 11.1 times more likely to meet European Union DHA recommendations.[13]

Other work has shown that supplementation with 200mg DHA from mid-pregnancy also helped to maintain the mother's DHA levels both later in pregnancy (at 37 weeks gestation) and three months after birth.[36] Equally, research by Sherry and colleagues (2015)[37] found that 200mg or 400mg DHA taken four to six weeks after birth improved maternal breast milk and infant plasma DHA levels which are needed for brain development.

Given that the mother is the main provider of a child's DHA when in utero and breastfeeding,[38] it is important for health professionals to be aware of DHA pregnancy guidelines. These can be communicated to women of childbearing age, along with suitable strategies to achieve these. Interestingly, findings from a study of 118 pregnant women showed that only 34% had received information about DHA, yet 68% said that they would like to know more.[39]

This paper has shown that the role of DHA in supporting the offspring's brain and eye development looks promising, particularly when taken in the third trimester and after birth. Other work also points towards DHA having a role in improving motor (movement) development,[40] infant sleeping patterns,[41] body composition and insulin sensitivity levels.[42] There is also emerging evidence that low omega-3 levels in late pregnancy could be a risk factor for postpartum depression.[43]

Further studies now need to integrate the use of biological biomarkers to assess DHA status alongside dietary assessment tools. It is also important that future studies record supplement compliance, ideally following Consolidated Standards of Reporting Trials[44] guidelines to do this, as this could affect DHA status and conclusions drawn from studies.

## CONCLUSIONS

DHA is an essential fatty acid with increasingly important roles during pregnancy and lactation. While DHA can be obtained from dietary sources, low bioavailability, high n-6 intakes from Western diets and concerns about oily fish consumption during pregnancy can all act as potential barriers to getting the proportions needed during this important life phase.

Considering this, topping up habitual intakes with a supplement containing DHA seems to be the most effective approach in terms of safely achieving European recommended levels of intake. Health professionals can play a key role in communicating this information to women during pregnancy and lactation, especially those with lower education and income levels who are most at risk of shortfalls in DHA.

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