Omega-3 fatty acid supply in pregnancy for risk reduction of preterm and early preterm birth

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This clinical practice guideline on the supply of the omega-3 docosahexaenoic acid and eicosapentaenoic acid in pregnant women for risk reduction of preterm birth and early preterm birth was developed with support from several medical-scientific organizations, and is based on a review of the available strong evidence from randomized clinical trials and a formal consensus process. We concluded the following. Women of childbearing age should obtain a supply of at least 250 mg/d of docosahexaenoic+eicosapentaenoic acid from diet or supplements, and in pregnancy an additional intake of ≥100 to 200 mg/d of docosahexaenoic acid. Pregnant women with a low docosahexaenoic acid intake and/or low docosahexaenoic acid blood levels have an increased risk of preterm birth and early preterm birth. Thus, they should receive a supply of approximately 600 to 1000 mg/d of docosahexaenoic+eicosapentaenoic acid, or docosahexaenoic acid alone, given that this dosage showed significant reduction of preterm birth and early preterm birth in randomized controlled trials. This additional supply should preferably begin in the second trimester of pregnancy (not later than approximately 20 weeks' gestation) and continue until approximately 37 weeks' gestation or until childbirth if before 37 weeks' gestation. Identification of women with inadequate omega-3 supply is achievable by a set of standardized questions on intake. Docosahexaenoic acid measurement from blood is another option to identify women with low status, but further standardization of laboratory methods and appropriate cutoff values is needed. Information on how to achieve an appropriate intake of docosahexaenoic acid or docosahexaenoic+eicosapentaenoic acid for women of childbearing age and pregnant women should be provided to women and their partners.

Key words: diet record, docosahexaenoic acid, fish oils, omega-3 polyunsaturated fatty acids, pregnancy nutrition, preterm birth

Introduction

Many etiologic factors are associated with risk of preterm birth (PTB) at <37 weeks and early PTB at <34 weeks.[1] However, compelling data demonstrate that higher supply and status in pregnant women of the omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) typically found in fish and fish oils, namely docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), reduce the risk of PTB, and even more substantially reduce the risk of early PTB.[2,3] Given the substantial impact of PTB and especially early PTB on both clinical outcomes and economic costs, obstetricians and other health care professionals caring for women before and during pregnancy need advice on safe, effective, and affordable approaches regarding intake of omega-3 long-chain fatty acids to reduce PTB and early PTB. Therefore, we developed a clinical practice guideline based on the existing evidence. The guideline is intended for all women of childbearing age and for all pregnant women regardless of whether they are at risk for PTB, either spontaneous or induced.

EDITOR'S CHOICE

Method

The guideline development was supported by the charitable Child Health Foundation (Stiftung Kindergesundheit, www.kindergesundheit.de) based at the Ludwig Maximilian University of Munich Hospitals. The guideline development was led by a steering committee (I.C., S.E.C., B.K.) with the support of a scientific manager. Medical-scientific associations in related fields, a global parent organization with a special focus on preterm infants, and renowned experts from all continents were invited to contribute to the guideline development (see list of authors). The steering committee drafted a summary of the evidence and a set of questions and proposed conclusions. These were discussed at an online consensus meeting on May 5, 2023, followed by anonymous online voting on the proposed 10 conclusions. An additional voting was conducted for an eleventh conclusion addressing information dissemination to women and their partners, which was developed during the process. Support of >95% of the guideline group members for a given conclusion was considered as "strong consensus", >75% to 95% as "consensus", >50% to 75% as "majority approval", and <50% as not supported. This was based on the medical guideline standards of the Association of the Scientific Medical Societies in Germany,[4] which have been adopted by academic societies across Europe.[5] The guideline text was drafted by the steering group, shared with all members and supporting organizations, revised with incorporation of the suggestions made, and finally approved by all members.

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Effective strategies to prevent preterm birth are currently limited, and identifying women at risk of preterm birth remains a challenge

PTB/early PTB may be spontaneous or physician-initiated in response to maternal or fetal conditions such as hypertensive disorders of pregnancy or fetal growth restriction. The pathophysiology of PTB appears to vary between patients, and there are many well-known risk indicators for spontaneous PTB/early PTB, including but not limited to history of spontaneous PTB, short cervical length, maternal smoking, and specific demographic and biomarker profiles.[1,6–9] A recent prognostic model derived from machine learning could predict close to half of PTBs.[10] However, this finding highlights that most PTBs/early PTBs occur in women with no known risk factors. Moreover, even if pregnancies at risk could all be identified, there are limited options for preventing spontaneous PTB. Progesterone has been extensively studied for the prevention of PTB. Natural vaginal micronized progesterone significantly decreases the risk of PTB in case of short cervix in singleton and twin pregnancies.[11,12] Low-dose aspirin has been evaluated in meta-analyses and systematic reviews for the purpose of prevention of preeclampsia. The results suggest that women receiving aspirin have a slightly lower occurrence of PTB by approximately 10%, in addition to lower rates of preeclampsia.[13,14]

Because most PTBs are not predictable neither preconceptionally nor during pregnancy, strategies to lower the incidence of PTB have aimed to improve maternal health and nutrition, avoid high-risk behaviors (eg, smoking), provide nutritional–lifestyle counseling, and lower the workload for women with stressful jobs.[15,16]

Omega-3 long-chain polyunsaturated fatty acid supply reduces the risk of preterm birth and early preterm birth

The importance of good nutrition in pregnancy is well-accepted.[17] The International Federation of Gynecology and Obstetrics (FIGO) Nutrition Checklist was developed to help obstetrical care providers counsel their patients.[18,19] Over the last 25 years, evidence has accumulated that intake of omega-3 LCPUFA can reduce the burden of PTB and early PTB. The first evidence came from a multicenter, randomized, placebo-controlled trial published in 2000 that included 19 hospitals across Europe. Women with a history of PTB were provided fish oil capsules containing 2.7 g of omega-3 LCPUFA including 900-mg/d DHA and 1200-mg/d EPA from 20 weeks of gestation.[20] Supplementation reduced recurrent PTB from 33% to 21% and early PTB from 14.9% to 10.6% and delayed delivery.[20] Two later placebo-controlled trials of high DHA supplementation (600-mg/d DHA or 800-mg/d DHA plus 100-mg EPA) were conducted in women at low risk for PTB with the goal to assess PTB risk reduction in these populations. Both found a significant reduction in early PTB as a secondary outcome among women with low intakes and low blood levels of omega-3 LCPUFA.[21,22]

A 2018 Cochrane Review led by Middleton et al[23] examined 70 randomized controlled trials (RCTs) (19,927 women) that evaluated omega-3 polyunsaturated fatty acid (PUFA) supplementation during pregnancy. Twenty-seven studies provided data on PTB and 11 on early PTB. The review found strong evidence based on multiple high-quality studies that pregnant women assigned to consume fish, fish oil, DHA, or DHA+EPA, or given dietary advice to consume foods with omega-3 PUFA had an 11% risk reduction of all-cause PTB at <37 weeks (risk ratio [RR], 0.89; 95% confidence interval [C], 0.81–0.97), and a 42% risk reduction of all-cause early PTB at <34 weeks (RR, 0.58; 95% CI, 0.44–0.77) compared with controls/placebo.[23] An analysis by etiology (ie, spontaneous vs physician-induced PTB) was not performed. The doses of DHA+EPA ranged from 200 to 2700 mg/d; however, the results were largely driven by trials that provided >500 mg/d of DHA.[23] Middleton et al[23] emphasize that their results were consistent with earlier systematic reviews on the topic that included fewer trials. Given that the evidence was deemed to be strong, additional studies comparing DHA or DHA+EPA with placebo in relation to PTB are very unlikely to change the confidence in the estimate of effect.

In 2022, Best et al[3] published results of an update of the 2018 Cochrane Review that included additional randomized trials, with a total of 36 trials (23,726 women) evaluated for PTB and 12 trials (16,782 women) evaluated for early PTB. High-certainty evidence (ie, evidence with high confidence that the true effect lies close to the estimated effect) showed a 12% reduction of PTB (RR, 0.88; 0.81–0.95) and a 35% reduction of early PTB (RR, 0.65; 0.46–0.92).[3]

Findings of trials published after the 2018 Cochrane Review

When the Cochrane Review was published, 2 randomized clinical trials were in progress with the primary aim of determining if high-dose DHA supplementation could reduce the incidence of early PTB regardless of etiology.[24,25] In both trials, supplementation started early in the second trimester of pregnancy. Unlike the trials included in the 2018 Cochrane Review, they were conducted after prenatal supplements containing DHA were widely marketed and used. In both trials, only women with low baseline DHA status had a lower rate of early PTB when assigned to a higher dose of DHA or DHA+EPA compared with placebo/low-dose DHA.

One of those trials, the "Omega-3 to Reduce the Incidence of Prematurity" (ORIP) trial, compared 800-mg DHA plus 100-mg EPA with placebo (a vegetable oil) in 5517 Australian women. Although the primary analysis did not find a reduction in the incidence of early PTB with DHA+EPA supplementation relative to placebo,[25] a secondary analysis identified that pregnant women with singleton pregnancies who had very low omega-3 status at baseline (defined as

total omega-3 fatty acids ≤4.1% of total fatty acids in whole blood) were at increased risk for early PTB and benefited from supplementation.[26]

The other trial ("Assessment of DHA on reducing early preterm birth" [ADORE]) was a comparative effectiveness trial conducted in the United States, wherein an algal supplement of 1000-mg/d DHA was compared with 200-mg/d DHA in 1100 pregnancies.[24] The higher dose reduced early PTB (Bayesian posterior probability [pp] =0.81); however, a secondary analysis showed that the reduction was for the 43% of women who entered the trial with low baseline DHA status (n=468/1100). Among women with low baseline DHA status, defined as red blood cell (RBC) phospholipid DHA content <6% of total fatty acids, the rate of early PTB was reduced by 51.2%, from 4.1% to 2.0%. A more conservative Bayesian analysis estimated a 47.9% reduction in RR of early PTB compared with the group assigned to 200-mg/d of DHA (from 4.8% to 2.5%; pp=0.93).[24] In women assigned to the higher dose, the risk reduction of early PTB was 65% (from 3.45% to 1.2%).[27] The higher dose also reduced PTB at <37 weeks as a secondary outcome (pp=0.95).

Another large trial conducted in China and published in 2019 assigned 5531 participants to 3 arms: 1 with high-dose fish oil (2-g/d DHA+EPA), 1 with less fish oil (0.5-g DHA+EPA), and 1 with olive oil. Although the trial did not find that fish oil prevented PTB, the overall rates of PTB were very low in this trial.[28] Previously, Olsen et al[29,30] reported longer gestation among supplemented women who reported consuming less fish and therefore had a lower intake of DHA and EPA.

Collectively, the results of the trials, which were designed to evaluate PTB, early PTB, and gestational age at delivery, indicate that supplementation benefits women with lower baseline DHA or total omega-3 fatty acid status by reducing the risk of PTB and early PTB. Although most studies did not distinguish between physician-induced and spontaneous PTB, the available evidence indicates a benefit in reducing spontaneous PTB (as described further in the following section).

Evidence suggesting that docosahexaenoic acid or docosahexaenoic+eicosapentaenoic acid protects against spontaneous preterm birth/early preterm birth and plausible physiological mechanisms

In the combined subsections of the European multicenter trial, in an analysis accounting for elective deliveries, supplementation with EPA+DHA delayed spontaneous delivery, with a proportional hazards ratio of 1.22 (95% CI, 1.07−1.39; *P*=.002).[20] There was no difference in preeclampsia occurrence, which frequently results in physician-initiated delivery. The findings of this study are supported by the 2018 Cochrane Review of 27 relevant RCTs comprising 10,304 participants, which found that omega-3 LCPUFAs reduced the risk of preterm prelabor rupture of membranes by 47% and of premature rupture of membranes by 59%, but did not influence the risk of preeclampsia.[23] In the ADORE trial, 22% (2/9) of early PTBs were spontaneous in participants assigned to 1000 mg/d, whereas 83% of early PTBs were spontaneous (10/12) in the group assigned to 200-mg/d DHA, suggesting that DHA may reduce the risk of spontaneous early PTB.[24]

Spontaneous PTB has been linked to infections and intraamniotic and cervical inflammation, with increases in proinflammatory cytokines and fetal T-cell activation proposed as a trigger for preterm labor.[1,31] Studies have shown that biomarkers linked to inflammation assessed before 20 weeks of gestation are associated with spontaneous preterm labor.[32−35] DHA and EPA are precursors for antiinflammatory products that are formed by the activity of COXs (cyclooxygenases), LOXs (lipoxygenases), and CYP (cytochrome P450) enzymes, the same enzymes that produce inflammatory products from the omega-6 fatty acid, arachidonic acid. Lipid biomarkers formed by LOXs and CYP pathways have been found to predict spontaneous PTB.[36] In an early study, Olsen et al[37] suggested that increased intake of EPA+DHA in pregnant women consuming more fish may prolong gestation by inhibiting the production of dienoic prostaglandins, primarily prostaglandin F2 alpha and prostaglandin E2 (PGE2), which are mediators of uterine contractions and cervical ripening. It is now generally accepted that DHA and EPA compete with arachidonic acid to inhibit the production of proinflammatory eicosanoids using COX and increase the production of antiinflammatory leukotriene B5 and prostaglandin F3 instead of inflammatory leukotriene B4 and PGE2.[38] DHA supplementation changes the balance between omega-3- and omega-6-derived mediators, which may reduce or prevent the inflammatory process associated with labor.[24] This is a plausible mechanism by which fish, fish oil, and supplements of DHA or DHA +EPA reduce spontaneous early PTB.

Sources of docosahexaenoic acid and intake

Fish is an excellent source of DHA and EPA, particularly oily fish (eg, salmon, mackerel, herring, tuna, sardines, anchovies), whereas egg yolks, liver, and poultry also provide small amounts of DHA.[39−41] Table 1 shows the approximate amounts of DHA in food sources, whereas the Supplemental Table presents a more complete list. Specialty foods with added DHA or eggs from chickens fed DHA may also be available for purchase. Globally, high blood levels of the omega-3 fatty acids DHA and EPA are associated with habitual high fish consumption.[42] Previously, a DHA intake of at least 200 to 250 mg/d was recommended for pregnant women to meet nutritional needs (Table 2[43−49]), but this level of intake has not been achieved in most populations. For example, among 47 high-income and 128 low- and middle-income countries, 64% had a mean DHA intake <200 mg/d in the adult population, with the lowest intake found in sub-Saharan African and Central and Southern Asian populations.[50] US pregnant women consume little fish (mean ∼50 g/wk), with 10% to 20% consuming no fish at all.[51] Much higher mean seafood intakes of 184 g/wk were reported for

TABLE 1
Categories of selected foods based on content of omega-3 eicosapentaenoic and docosahexaenoic acid (mg/100 g)

>1000 mg/100 g	500–1000 mg/100 g	250–500 mg/100 g	<250 mg/100 g
Herring (Atlantic, kippered): 2150	Sardine (Atlantic, canned): 982	Carp (cooked): 451	Grouper (mixed species, cooked): 248
Salmon (Atlantic, farmed, cooked): 2150	Bass (striped, cooked): 967	Pike (walleye, cooked): 398	Halibut (Atlantic and Pacific, cooked): 235
Anchovy (European, canned): 2052	Trout (mixed species, cooked): 936	Pollock (Alaska, cooked): 333	Liver, beef (grass-fed): 234
Herring (Atlantic, cooked): 2009	Salmon (sockeye, cooked): 859	Tuna (skipjack, cooked): 328	Cod (Atlantic, cooked): 158
Mackerel (Pacific and jack, cooked): 1853	Bass (fresh water, mixed species, cooked): 763	Liver, lamb (grass-fed): 326	Tilapia (cooked): 135
Salmon (Atlantic, wild, cooked): 1841	—	Perch (mixed species, cooked): 324	Tuna (fresh, yellowfin, raw): 100
Mackerel (Spanish, cooked): 1246	—	Hake (frozen, cooked): 280	Catfish (farmed, cooked): 89
Gilthead bream: 1160	—	Tuna (light, canned): 270	Cod (Pacific, cooked): 80
Salmon (coho, wild, cooked): 1059	—	—	Eggs (chicken, whole, cooked): 58
—	—	—	Chicken, dark meat (roasted): 50

Data extracted from Supplemental Table.[39-41]

Cetin. Omega-3 fatty acid supply in pregnancy for risk reduction of preterm and early preterm birth. Am J Obstet Gynecol MFM 2023.

TABLE 2
Organizations previously providing recommendations for docosahexaenoic or docosahexaenoic+eicosapentaenoic acid intake during pregnancy

Organization	Amount of DHA or DHA+EPA per day for women of childbearing age (general population)	Amount of DHA or DHA+EPA per day during pregnancy
Food and Agriculture Organization of the United Nations,[43] 2010	250-mg DHA+EPA	≥200-mg/d of DHA toward total 300-mg n-3 EPA+DHA
AFFSA,[44] France, 2010 and ANSES,[45] France, 2011	250-mg DHA/500-mg DHA+EPA	250-mg DHA/500-mg DHA+EPA
European Food Safety Authority,[46] 2010	250-mg DHA+EPA	250-mg DHA+EPA and additional 100–200-mg DHA
International Society for the Study of Fatty Acids and Lipids,[47] 2004	≥500-mg DHA+EPA	≥200-mg DHA
Perinatal Lipid Intake Working Group,[48] 2007	—	≥200-mg DHA
Chinese Nutrition Society,[49] 2014	250–2000-mg DHA+EPA	250-mg EPA+DHA, of which 200 mg should be DHA

AFFSA, Agence française de sécurité sanitaire des aliments; *ANSES*, Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail; *DHA*, docosahexaenoic acid; *EPA*, eicosapentaenoic acid.

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pregnant women in Sweden.[52] Supplements containing fish oil or algal oil are other sources that increase DHA levels in pregnant women.[24,25,53]

Who has low docosahexaenoic and eicosapentaenoic acid status in pregnancy, and does it matter?

DHA and EPA status may be determined by laboratory analysis of blood lipids. A variety of blood lipid measures are available. These include total plasma fatty acids, plasma lipid fractions (eg, phospholipids, triglycerides), whole blood (dried or liquid), or blood cells (erythrocytes, leukocytes, platelets). Although n-3 LCPUFA levels (percentage of total) are highly intercorrelated among these lipid pools, there is no general agreement on which lipid pool to use clinically to identify low status.[54] The recent trials that identified a benefit for women with low status used a blood spot or isolated phospholipids from packed RBCs. One laboratory that compared both sample types[55] proposed a common metric for baseline RBC DHA of 5% as the threshold above which women have the lowest risk for early PTB.[56] An RBC DHA of 5% is equivalent to the approximately 6% RBC phospholipid DHA used as a cutoff for baseline DHA status in the ADORE trial to compare the effect of baseline status and adherence to the 1000-mg DHA dose. Participants of the ADORE trial below the DHA threshold at baseline who adhered to the regimen had a 58% reduction in PTB and a 65% reduction in early PTB.[27] Participants with a baseline status above the threshold had low rates of PTB and early PTB on the 200-mg dose. Adherence to the high-dose regimen reduced PTB by 50% but had no effect on the already low rate of early PTB.[27]

Although laboratory assessment for DHA status could be incorporated into the already established clinical testing protocol in pregnancy, the capacity to routinely assess DHA status in pregnant women is currently not present in every country worldwide. In addition, a health economic analysis of the added benefits vs costs for collecting and analyzing blood samples is not available.

Alternatively, assessment of habitual DHA intake could be a promising way to identify women who would benefit from high-dose DHA supplementation to reduce PTB and early PTB. In both the ADORE trial and the Prenatal DHA and Neurofunctional Development (PANDA) trial,[57] which compared 800-mg/d with 200-mg/d DHA, women completed a 7-question food frequency questionnaire (FFQ) to assess DHA intake at baseline (DHA-FFQ). Women consuming <150 mg/d of DHA on average benefited from assignment to high-dose DHA (800 or 1000 mg) compared with the lower dose of 200 mg/d, with reduced early PTB (pp=0.99) and PTB (pp=0.97).[58] This is consistent with an earlier observational study by Olsen and Secher,[59] who found that the relation between n-3 LCPUFA intake and lower PTB risk is strongest in women with an estimated daily intake of n-3 LCPUFA <150 mg. A study in mother–infant pairs in the United States showed maternal and cord blood n-3 PUFA concentrations significantly higher in college-educated than in less educated women after adjustment for relevant confounders.[60] In another intervention study, women in the United States with an FFQ-based estimated intake <150 mg/d of DHA from combined diet and supplements were more likely to have lower income, less education, and be non-Hispanic Black or of Hispanic ethnicity than women with a higher intake.[58] These findings underline the need for efforts targeted to women of lower socioeconomic status or at-risk ethnic groups. It is worth noting that most women who were consuming >150 mg/d of DHA in the latter study were achieving this intake at least partly via supplementation. The DHA-FFQ has been validated against RBC phospholipid DHA and assessed using a secure online survey (REDCap survey; Vanderbilt University, Nashville, TN).[61,62]

The relationships between DHA intake and the risk of PTB and early PTB have been assessed by the DHA-FFQ; however, other validated FFQs could also be used. Daily intakes of marine n-3 LCPUFA assessed in pregnant women in Denmark through a self-administered questionnaire focusing on breakfast and lunch food items correlated with the RBC phospholipid long-chain n-3 PUFA to arachidonic acid ratio.[63] Country-specific DHA-FFQs have been validated against DHA status during pregnancy in China and Japan,[64,65] and there is a validated FFQ to assess risk of low omega-3 fatty acid intake in adults in Switzerland.[66] Further evaluation of the value of simple dietary assessment approaches for predicting low DHA status and increased risk of PTB in other populations with different dietary habits would be useful.

Safety of docosahexaenoic acid or docosahexaenoic+eicosapentaenoic acid intakes

No upper limit has been established above which DHA and EPA intakes in pregnancy would be potentially harmful. The early prophylactic and therapeutic trials of Olsen et al[20] provided 2.7 g/d and 6.1 g/d, respectively, of omega-3 LCPUFA, mostly DHA and EPA. They found an increase in postterm birth with these very high doses continuing to term, but no serious adverse effects linked to hypothetical biological effects of fish oil were identified, including macrosomia, vaginal bleeding, intracranial hemorrhage in the neonate, or maternal blood loss.[20] The 2018 Cochrane Review concluded that omega-3 LCPUFA *probably* increased the incidence of postterm pregnancies, but found no differences for serious adverse events for mothers. As for their offspring, there was evidence of protection against serious adverse events including PTB, neonatal death, and need for intensive care.[23] Earlier reviews that addressed fat and fatty acid requirements during pregnancy and lactation reported that pregnant women have been provided up to 2.7 g of omega-3 LCPUFA with no observed adverse effect.[43,67] The United States Food and Drug Administration (FDA) concluded in 2004 that intake of DHA and EPA up to 3 g/d (together or alone) from the combination of diet and dietary supplements is safe for consumers, and further considered that

supplementation with up to 2 g/d of DHA and EPA combined is safe, in addition to intakes from foods.[68] The European Food Safety Authority (EFSA) stated in 2012 that daily intake of up to 5 g EPA+DHA, 1.8 g of EPA alone, or 1.0 g of DHA alone does not raise any safety concerns.[69]

In the ADORE trial, the higher DHA dose of 1000 mg/d (1 g/d) was associated with fewer serious adverse events, such as maternal chorioamnionitis, premature rupture of membranes, and pyelonephritis, and in the neonate, fewer feeding, genitourinary, and neurologic problems.[24] The ORIP trial (paradoxically) reported a higher RR of early PTB among women who began the trial with high DHA status and who were provided the supplement compared with those who received the placebo.[25]

Current recommendations for docosahexaenoic acid or docosahexaenoic +eicosapentaenoic acid intakes in pregnancy

The World Health Organization, EFSA, the United States Environmental Protection Agency, FDA, and FIGO all recommend that pregnant women consume fish and seafood for general nutritional support.[17,70–72] The American College of Obstetricians and Gynecologists (ACOG) recommends that women who are pregnant or planning to conceive consume 8 to 12 ounces (227–340 g) of seafood per week.[73] However, none of these bodies specifically mention that fish provides DHA and EPA that may reduce the risk of PTB and early PTB. The Perinatal Lipid Intake Working Group recommends at least 200 mg/d of DHA for pregnant women and those of childbearing age, but also does not tie the recommendation to PTB or early PTB.

Although many organizations recommend DHA (or DHA plus EPA) intake during pregnancy in recognition of its potential importance as a nutrient (Table 1),[43–49] the rationale for these recommendations is not the reduction of PTB and early PTB. Most recommend an average daily intake of 200 to 250 mg/d of DHA or DHA+EPA, whereas the Food and Agriculture Organization of the United Nations recommends 300-mg/d DHA+EPA and the EFSA 350 to 450-mg/d DHA+EPA for pregnant women[43] (Table 1). Other groups, including FIGO and ACOG, recommend regular seafood (fish) consumption, which would effectively provide about this amount of DHA.[17,73]

Currently, only 2 countries link the recommendation for DHA intake in pregnancy to reduction of PTB. The Australian National Health and Medical Research Council states that supplementation with 800-mg/d DHA and 100-mg/d EPA may reduce the risk of PTB among women who are low in omega-3 fatty acids.[74] The Polish Society of Gynecologists and Obstetricians recommends an intake of at least 200 mg/d of DHA in all pregnant women, with a higher dose in women consuming small amounts of fish during pregnancy and in the preconception period, and 1000 mg/d of DHA for women at risk of PTB.[75]

In 2022, the International Society for the Study of Fatty Acids and Lipids issued a statement on omega-3 fatty acids to reduce PTB. The statement suggests that women with a low habitual intake of DHA and EPA or low status of DHA and EPA may benefit most from DHA and EPA supplementation with respect to risk reduction of PTB and early PTB.[3] The statement recommends that these women be supplemented with a total of approximately 1000 mg of DHA and EPA to reduce the overall risk of early PTB at <20 weeks of gestation. To implement this guidance, there must be a robust method for identifying women with low habitual intake or status. As summarized above, one approach is to measure DHA status in blood samples, and data are available to harmonize results from different analytical approaches. Another is to assess dietary intake of DHA by validated questionnaires.

Assessing DHA intake through a structured questionnaire applied at the first obstetrical visit is a promising approach to identify women who could effectively lower their risk of early PTB and PTB by consuming high-dose DHA or DHA+EPA. Women consuming <150 mg/d of DHA or DHA+EPA from food and supplements appear to be at the highest risk of PTB.[58,59] The most recent trials provided 1000[24] and 800 mg/d[25] of DHA, respectively; however, 600 mg/d was very effective in a smaller trial of women with low baseline DHA status conducted before the wide availability and use of prenatal supplements with DHA.[21]

Evidence-based information on how to achieve an appropriate intake of DHA or DHA+EPA among women of childbearing age and pregnant women should be provided to women and their partners, ideally both verbally and in writing. Consistent with EFSA's guidance, this panel recommends that women of childbearing age consume a regular intake of at least 250 mg/d of DHA+EPA. This level will help provide for their nutritional needs and establish a good DHA status should they become pregnant. It is very difficult to achieve an average intake ≥250 mg/d of DHA or DHA+EPA without consuming seafood or a supplement of DHA or fish oil. FIGO has recommended that pregnant women aim at preferentially eating small fishes (eg, bluefish, anchovies, sardines) because of a lower risk of methylmercury contamination compared with large, predatory fishes.[17]

The currently available information does not show an appreciable benefit of taking high-dose omega-3 fatty acid supplementation in pregnant women who consume >150 mg/d of DHA habitually before or early in pregnancy, or who have higher blood DHA status (as defined above) early in pregnancy. However, it is important to note that it is very difficult to achieve an average intake >150 mg/d of DHA without consuming seafood or a supplement of DHA or fish oil. This expert panel recommends that pregnant women who are consuming >150 mg/d DHA or have higher blood DHA status early in pregnancy and are at low risk of spontaneous early PTB be encouraged to consume ≥250 mg/d of DHA+EPA

TABLE 3
Summary of consensus recommendations from this expert panel

Population	Recommendation
General adult population, including women of childbearing age	Average intake of ≥250 mg/d of DHA+EPA[a] omega-3s from foods and/or from supplements
All pregnant women	Average intake of ≥250 mg/d of DHA+EPA and an additional intake of ≥100−200 mg/d of DHA[a]
Pregnant women with low DHA intakes or blood levels at the beginning of pregnancy[b]	Average intake of approximately 600−1000 mg/d of DHA+EPA, or DHA alone, preferably beginning in the second trimester of pregnancy and not later than approximately 20 weeks' gestation, and continuing until childbirth or approximately 37 weeks' gestation
General population and pregnant women	Intakes up to 1000 mg/d of DHA+EPA, or up to 1000 mg/d of DHA alone, do not raise safety concerns

DHA, docosahexaenoic acid; *EPA*, eicosapentaenoic acid.

[a] In line with the recommendations of the European Food Safety Authority[46]; [b] Identification of women at increased risk of preterm and early preterm birth due to a low DHA intake and/or low DHA blood levels is achievable by screening with a few questions on dietary intake of foods rich in DHA and EPA and on use of omega-3 supplements, or by blood measurement.

Cetin. Omega-3 fatty acid supply in pregnancy for risk reduction of preterm and early preterm birth. Am J Obstet Gynecol MFM 2023.

recommended for women of childbearing age and to have an additional intake of at least 100 to 200 mg/d of DHA, consistent with EFSA's guidance for omega-3 intake by pregnant women.[46]

Women who consume <150 mg/d of DHA or have low blood DHA early in pregnancy need advice to help them consume DHA or DHA+EPA in the range of 600 to 1000 mg/d until at least 37 weeks of gestation. The easiest way to accomplish this is with a supplement that contains DHA or DHA+EPA. Advice should be offered from the beginning of pregnancy onward, either with individual counseling, in small groups, and/or with digital health intervention tools[17,76] while taking into account that many women who have spontaneous PTB or early PTB have no known risk factors. DHA supplements induce costs, and many women do not enjoy taking them because of pill size or unpleasant aftertaste. Issues of cost and adherence can be addressed for women whose risk of early PTB can be reduced by higher-dose supplementation between 600 and 1000 mg/d. A personalized approach to recommendation may improve adherence and compliance.

The highest amount of n-3 LCPUFA supplied in a randomized clinical trial of pregnancy is 6.1 g/d in the Olsen et al[20] therapeutic trial without serious adverse events but with increased risk of late term gestation. As summarized above, there is no evidence to indicate that >1000 mg/d (1 g/d) would enhance the effect of DHA or DHA+EPA on reducing early PTB. Practical implementation of a strategy of supplementation with 600 to 1000-mg omega-3 LCPUFA for women at high risk requires informing obstetricians and other health care professionals who consult women and their partners before and during pregnancy. All health care providers should be aware of maternal nutritional issues[17] and when supplementation is advisable. Future development of policies to ensure availability of omega-3 fatty acids to women are an important next step, including women who have no or improper access to health care and healthy nutrition and women in low- and middle-income countries.

Conclusions

The panel agreed on the following conclusions (summarized in Table 3[46]):

1. Intakes of up to 1000 mg/d of DHA and EPA or up to 1000 mg/d of DHA alone do not raise safety concerns in the general population or in pregnant women (consensus, supported by 89.5% of votes).
2. Observational studies and RCTs in pregnant women show that lower intakes and lower blood levels of fish and of the omega-3 fatty acids DHA and EPA found in fish are associated with significantly increased risk of PTB and early PTB (consensus, supported by 85%).
3. Women of childbearing age should aim to obtain a regular supply of omega-3 fatty acids from foods providing these fatty acids, including fish and oily fish, and/or from supplements providing DHA and EPA or DHA alone (strong consensus, supported by 100%).
4. For the general population, including women in their childbearing years, a regular intake of at least 250-mg/d DHA+EPA, as recommended by the EFSA, is desirable (strong consensus, supported by 100%).
5. For pregnant women, an additional intake of at least 100 to 200 mg/d of DHA, as recommended by the EFSA, is desirable (strong consensus, supported by 100%).
6. Pregnant women with a low DHA intake and/or low DHA blood levels are at increased risk of PTB and early PTB and should receive

a regular supply of approximately 600 to 1000 mg/d of DHA+EPA or DHA alone, according to results of RCTs demonstrating significant reduction of PTB and early PTB (consensus, supported by 90%).
7. This additional supply should preferably begin in the second trimester of pregnancy and not later than approximately 20 weeks of gestation (consensus, supported by 85.0%).
8. High-dose supplementation with the goal of risk reduction for PTB should continue as long as there is a risk of PTB (ie, until approximately 37 weeks of gestation) or until childbirth if before 37 weeks (consensus, supported by 80%).
9. Identification of women at increased risk of PTB and early PTB due to low DHA intake and/or low DHA blood levels is achievable by screening with a few questions on dietary intake of foods rich in DHA and EPA and on use of omega-3 supplements (consensus, supported by 90.0%).
10. DHA measurement from a blood lipid component is an additional option to identify women with low status; however, further standardization of laboratory methods and of appropriate cutoff values is needed (consensus, supported by 85.0%).
11. It is important to provide women of childbearing age, pregnant women, and their partners with evidence-based information, preferably both verbally and in writing, on how to achieve an appropriate intake of DHA or DHA+EPA during childbearing age and pregnancy (strong consensus, supported by 100%).

The panel also agreed on the following recommendations for further research:

1. Further evaluation of simple and practical screening approaches for identifying women before and during pregnancy with low long-chain omega-3 fatty acid intakes should be performed, with inclusion of populations with different dietary habits. Digital tools that may be included in electronic medical records and that allow for automatic categorization of women into low- and high-risk groups should be developed.
2. Standardization of laboratory methods for assessing DHA or DHA+EPA levels from blood samples and validation of cutoff values for predicting high risk of PTB and early PTB in different populations should be conducted.
3. The effects of targeted high-dose supplementation of DHA or DHA+EPA above the standard recommended intake of 200 to 250 mg/d should be evaluated in women at higher risk of spontaneous PTB (determined, eg, by a history of PTB, reduced cervical length, raised cervicovaginal fetal fibronectin, or other biomarkers).
4. Future studies on preventive strategies should aim to collect data separately for spontaneous and physician-induced PTB.
5. Studies should be performed to evaluate the feasibility of implementation and achievable effect sizes in low- and middle-income country populations.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2023.101251.

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