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CLINICAL TRIAL REPORT

# Docosahexaenoic acid (DHA) Supplementation During Pregnancy Reduces the Risk of Preterm Birth in Threatened Preterm Labor. The Multicenter Randomized Controlled Trial

Wiphawi Phattharachindanuwong[1], Sukanya Chaiyarach[1], Ratana Komwilaisak[1], Piyamas Saksiriwuttho[1], Chatuporn Duangkum[1], Kiattisak Kongwattanakul[1], Pilaiwan Kleebkaow[1], Termtem Waidee[1], Manasicha Pongsamakthai[2], Sathida Chantanavilai[2], Tunyatorn Srisataporn[2]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; [2]Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen, Thailand

Correspondence: Wiphawi Phattharachindanuwong; Sukanya Chaiyarach, Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, 40000, Thailand, Tel +66869077662; +66836760565, Email wiphawi.beer@gmail.com; sukancha@kku.ac.th



**Background:** Threatened preterm labor is a common reason for hospital admission, and DHA supplementation may lower the risk of preterm labor.

**Objective:** To compare the rates of premature birth between individuals with threatened preterm labor who received DHA and those who did not.

**Methods:** In this multi-center randomized controlled trial, the sample size was calculated to be 60 participants. Pregnant individuals who experienced threatened preterm labor at 24 to 34 weeks gestation were given either 1000 milligrams of DHA daily or no DHA supplement. The criteria for inclusion consisted of singleton pregnancies that had been diagnosed with threatened preterm labor, with no cervical change present. DHA supplementation was initiated when threatened preterm labor was diagnosed and continued until 37 weeks of gestation or until delivery, whichever occurred first. The main outcome was to compare the rates of premature births between the two groups. Moreover, we intended to evaluate the side effects of the DHA supplement along with the outcomes for neonates.

**Results:** Sixty-one pregnant individuals were enrolled and randomly assigned to two groups. Group 1 consisted of 30 participants, each receiving a daily intake of 1,000 milligrams of DHA supplement. Group 2, comprising 31 individuals, did not receive any supplemental DHA. The rate of preterm birth was 23.33% (7/30) and 25.81% (8/31) for the participant group receiving DHA and not receiving DHA, respectively, with a p-value of 0.82. The rate of low-birth-weight neonates was 13.33% (4/30) and 19.35% (6/31) for the participant group receiving DHA and not receiving DHA, respectively, with a p-value of 0.73. The overall results did not show any statistically significant differences. In addition, the rates of cesarean sections, peripartum infections, early postpartum hemorrhage, and NICU admissions did not show significant differences between the two groups.

**Conclusion:** Taking DHA supplements after a diagnosis of threatened preterm pregnancy does not decrease the actual rates of early or late preterm births. To reduce the risk of premature birth, DHA should be taken from the beginning of pregnancy, with a recommendation to start in the first trimester. This should ideally start in the second trimester, no later than around 20 weeks of gestation, and should continue until childbirth or approximately 37 weeks of gestation.

**Clinical Trial Registration:** https://register.clinicaltrials.gov/.

**Clinical Trials:** gov; ID: NCT06302023.

**Keywords:** docosahexaenoic acid, DHA, preterm birth, threatened preterm labor, omega-3 polyunsaturated fatty acids, pregnancy nutrition



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## Introduction

Preterm birth is described as a delivery that takes place prior to 37 weeks of gestation. As of 2020, the global incidence of preterm delivery is estimated to be between 4 and 16%.[1] In 2022, the rate of premature births in Health Zone 7 was 12.6%, making it the fourth highest in Thailand. The Department of Health aims to reduce the preterm birth rate to no more than 9%.[2] The incidence of premature birth at Srinagarind Hospital is 17%. The effects of premature birth cause morbidity and increased neonatal mortality rates.[3,4] Premature birth can be caused by several factors, including infections in the amniotic sac, endometrial infections, and urinary tract infections.[5] The pathology found that the condition was premature labor, which is related to creating inflammatory substances such as prostaglandins through communication between cells.[6] Previous studies have shown that Omega-3 fatty acids are essential unsaturated fatty acids. These nutrients are particularly important during pregnancy because they are essential for the development of the fetus's brain and retina.[7] It is vital in influencing the length of pregnancy and in reducing the risk of postpartum depression. The active compounds involved are Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Consequently, the US Food and Drug Administration (FDA) advises a daily DHA supplementation of no less than 200 milligrams throughout pregnancy.[8] DHA influences the onset and duration of the inflammatory process. Additionally, it enhances the expression of SIRT1, which plays a crucial role in endothelial relaxation and cell signaling. Pharmacokinetic studies of DHA administration indicate that the time taken to reach the maximum observed concentration is about six hours, while a steady-state concentration is achieved after 14 days of continuous daily intake of DHA.[9] DHA is derived from phospholipids in cell membranes and acts as a precursor for the synthesis of docosanoids, which possess anti-inflammatory properties. Research has examined DHA supplementation during pregnancy, specifically at doses of 800 milligrams and 600 milligrams per day. Findings show that compared to the placebo group, the group that received DHA supplementation experienced a notable decrease in the incidence of births occurring prior to 34 weeks of gestation.[10] There are limited studies on DHA supplementation in pregnant individuals experiencing threatened preterm labor. Therefore, the research team aims to study additional information. This study assesses the efficacy of DHA supplementation in pregnant individuals facing threatened preterm labor to lower the incidence of premature birth.

## Materials and Methods

### Study Setting and Design

This study is a multi-center randomized controlled trial in Srinagarind Hospital, Khon Kaen University, and Khon Kaen Hospital, Khon Kaen, Thailand. The study is registered on ClinicalTrials.gov (NCT06302023) and is no longer open for enrollment.

### Participants/Inclusion and Exclusion Criteria

In this trial, the inclusion criteria are singleton pregnancies between 24 and 34 weeks of gestational age for pregnant women diagnosed with threatened preterm labor (without cervical change).[11] Exclusion criteria include fetal anomalies, multiple pregnancies, premature rupture of membranes, placental disorders such as placenta previa, placental abruption, fetal growth restriction, and pregnancy complications like gestational diabetes mellitus, chronic hypertension, morbid obesity, and allergic reactions to DHA. Withdrawal criteria include loss to follow-up, indicated preterm birth, and pregnant women who wish to discontinue DHA supplementation.

### Study Methods

The study's details were communicated to participants, and they provided written informed consent prior to joining the study. This documentation included potential side effects associated with the medication, which encompassed: nausea and vomiting, acute hepatitis, bloating, and increased bleeding tendency. Participants were assured that their decision to join the study was entirely voluntary, and this choice did not affect their basic treatment rights. Furthermore, individuals had the right to withdraw from the study at any time without any repercussions. Participants were assigned to two groups through a pre-prepared randomization process, utilizing sealed envelopes. This involved block randomization with four blocks, stratified solely by maternal age (less than 35 years old and more than 35 years old). Group 1 (Experimental:

DHA supplement) consisted of pregnant women who were asked to take DHA 1000 milligrams of DHA per day at bedtime until delivery or until they reached 37 weeks of gestational age. Group 2 (No Intervention) consisted of pregnant women who did not receive any DHA supplement. After providing the necessary information and signing the consent form, the obstetric history and any medications taken during pregnancy were recorded by reviewing medical records and taking patient histories using a case record form. The researcher also requested contact information from participants. In the intervention group, participants used dietary supplements in capsule form, each containing DHA 1000 milligrams. Each participant was instructed to take one capsule daily at the same time, specifically before bedtime, until delivery or until they reached 37 weeks of gestational age. Within 1 to 2 weeks of receiving the medication, the researcher called to inquire about any side effects and compliance with the medication regimen. If any adverse symptoms occurred, participants could contact the researcher directly by telephone. Participants documented the adverse reactions they experienced in detail. Non-compliance was defined as taking less than 80% of the prescribed medication. Participant compliance was evaluated using self-reported data. In the control group, no additional interventions were provided beyond standard treatment. Uterine contractions were measured using a fetal monitoring device. The fetal monitoring machine is a GE Healthcare product. It will be installed to assess patients prior to their admission to the hospital. At the end of the research, data were collected on pregnancy outcomes, including gestational age at birth, route of delivery, intrapartum complications, postpartum hemorrhage, postpartum infection, and neonatal outcomes.

## Outcomes

The primary outcome is to compare the rates of premature births between the two groups. We also plan to evaluated the side effects of the DHA supplement and its impact on newborns.

## Sample Size

The sample size is determined using the formula for testing two independent proportions. A prior study assessed the impact of maternal DHA supplementation on early preterm birth in Australia and the US (L.N.Y.,2016). The results showed that DHA supplementation resulted in a 62% decrease in preterm birth rates among the treated group.[10] The sample size is calculated to be 27 per group, and with a 10% drop-out rate included, the total sample size required is 60.

## Statistical Analysis Plan

The baseline characteristics of the participants will be compared between those who received DHA supplements and those who did not. The analysis will present categorical data as numbers and percentages, using the Pearson chi-squared or Fisher's exact tests. Continuous data will be evaluated with the Shapiro–Wilk test to check for normality. If the data is normally distributed, it will be summarized as the mean and standard deviation (SD), and analyzed with an independent *t*-test. For non-normally distributed data, the median and interquartile range (IQR) will be reported, and the Mann–Whitney *U*-test will be used for analysis. A two-sided P-value below 0.05 will indicate statistical significance. We will report the median gestational age at delivery for both primary and secondary outcomes between the groups. The results were assessed through both intention-to-treat and per-protocol analyses. All data were analyzed with the Stata version 18.0 program.

# Results

Participants were enrolled between March 6, 2024 and October 7, 2024. Figure 1 Among the 418 pregnant women screened for eligibility, 357 were excluded for the following reasons: 108 had advanced cervical progression, 54 had twin or multiple pregnancies, 56 experienced preterm premature rupture of membranes, 48 had placental previa or placental accreta spectrum, 47 had pre-gestational or gestational diabetes mellitus, 35 had pregnancy-induced hypertension or primary hypertension, 16 had fetal anomalies, 16 had fetal growth restriction and, 3 had idiopathic thrombocytopenia. A total of 61 pregnant women were recruited and subsequently randomized into two groups. Group 1 consisted of 30 participants, each receiving a daily intake of 1000 milligrams of DHA supplement. Group 2, also comprising 31 individuals, did not receive any supplemental DHA. Participant baseline characteristics are presented in Table 1.

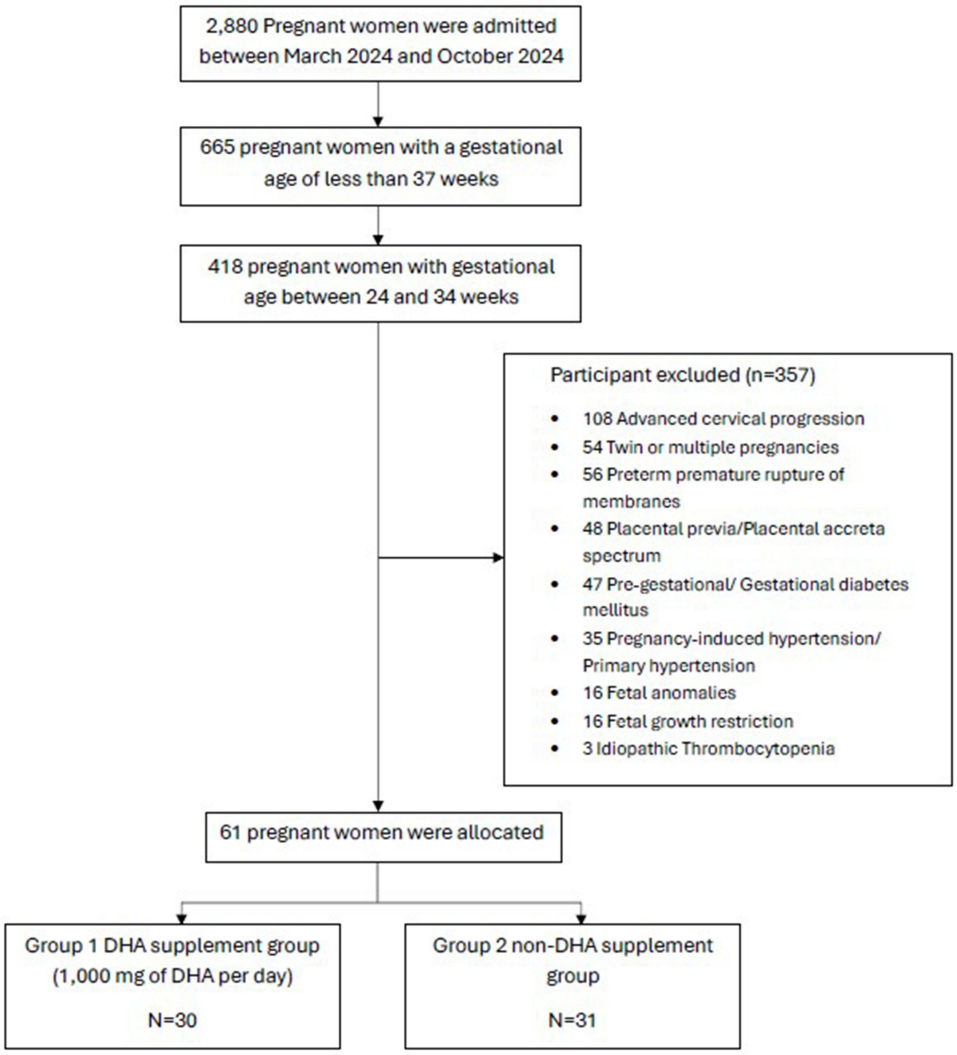


**Figure 1** Population flow.

The average age of mothers in the DHA-treated group was 29.8 years, compared to 29.45 years in the non-DHA-treated group. The ages of the pregnant participants varied between 19 and 41 years. All participants are residents of the northeastern region of Thailand. Among those receiving DHA, 70% (21/30) were multigravida, while 61.29% (19/31) in

**Table 1** Maternal Demographics and Clinical Characteristics (n=60)

| Characteristic | DHA Supplement (n=30) | Non-DHA Supplement (n=31) | P-value |
|---|---|---|---|
| Maternal age, mean (SD) | 29.8 (5.86) | 29.45 (6.17) | 0.822 |
| Multigravida, n(%) | 21 (70) | 19 (61.29) | 0.474 |
| Prior preterm birth, n(%) | 2 (6.67) | 2 (6.45) | >0.001 |
| Pre-pregnancy BMI[a], n(%) | | | >0.001 |
| - Underweight | 4 (13.33) | 4 (12.9) | |
| - Normal | 19 (63.33) | 19 (61.29) | |
| - Overweight | 5 (16.67) | 6 (19.35) | |
| - Obese | 2 (6.67) | 2 (6.45) | |

(*Continued*)

**Table 1** (Continued).

| Characteristic | DHA Supplement (n=30) | Non-DHA Supplement (n=31) | P-value |
|---|---|---|---|
| Total weight gain during pregnancy, n(%) | | | 0.172 |
| - Under recommendation | 4 (13.33) | 3 (9.68) | |
| - Within recommendation | 21 (70) | 25 (80.65) | |
| - Over recomendation | 5 (16.67) | 3 (9.68) | |
| - Late antenatal care, n(%) | 8 (26.67) | 9 (29.03) | 0.837 |
| Hb at enrollment, median (IQR[b]) (g/dL) | 11.6 (11.2, 12.2) | 11.5 (10.4, 12.4) | 0.644 |
| Anemia, n(%) | 6 (20) | 9 (29.03) | 0.413 |
| Underlying diseases, n(%) | | | |
| Thyroid disease | 1 (3.33) | 1 (3.23) | >0.999 |
| Short cervical length <25 mm, n(%) | 3 (10) | 3 (9.68) | >0.999 |
| Vaginal progesterone used during pregnancy, n(%) | 5 (16.67) | 6 (19.35) | 0.785 |
| Aspirin used, n(%) | 5 (16.67) | 6 (19.35) | 0.785 |
| Tocolytic, n(%) | | | 0.515 |
| - Calcium chanel blocker | 18 (60) | 21 (67.74) | |
| - Terbutaline | 5 (16.67) | 2 (6.45) | |
| - Magnesium sulfate | - | - | |
| - Multiple tocolytics | 7 (23.33) | 8 (25.81) | |
| Number of days received DHA, median (IQR) (days) | 29 (21, 49) | 0 | |

**Notes**: [a]Body Mass Index. [b]Interquartile Range.

the other group were multiparous. Both groups reported an equal history of preterm birth in prior pregnancies. The majority of participants in both groups had normal pre-pregnancy body mass index (BMI) and achieved appropriate total weight gain during pregnancy. The rate of pregnant women seeking late antenatal care was similar in both groups. The percentage of pregnant women with anemia was 20% (6/30) in the DHA-treated group and 29.03% (9/31) in the non-DHA-treated group. None of the participants consumed alcohol or smoked during pregnancy. The number of pregnant women with a short cervix who received vaginal progesterone was equal in both groups. Aspirin was administered for the prevention of preeclampsia in 16.67% (5/30) of participants in the DHA-treated group and 19.35% (6/31) in the non-DHA-treated group. The most commonly used tocolytics for inhibiting labor in both groups included various medications, such as calcium channel blockers and terbutaline. Pregnant women who received DHA showed good compliance with their medication intake. The median duration of DHA intake was 29 days, which surpassed the steady-state concentration. For the pregnancy and neonatal outcomes presented in Table 2. The rates of preterm birth were 23.33% (7/30) and 25.81% (8/31) for the participant group receiving DHA and not receiving DHA, respectively. The results were not statistically significantly different with a p-value of 0.82. The median gestational age at delivery is 37 weeks 6 days for the participant group receiving DHA and 37 weeks 5 days for the group not receiving DHA, with a p-value of 0.79.

**Table 2** Pregnancy and Neonatal Outcomes

| Outcome Measure | DHA Supplement (n=30) | Non-DHA Supplement (n=31) | P-value |
|---|---|---|---|
| Gestational age at birth, median (IQR) (days) | 265 (259, 269) | 264 (256, 270) | 0.7991 |
| Preterm birth, n(%) | 7 (23.33) | 8 (25.81) | 0.823 |
| Early preterm birth, n(%) | 1 (3.33) | 0 (0) | 0.305 |
| Neonatal birth weight, mean(SD) | 2897 (420.09) | 2890.16 (543.53) | 0.956 |
| Low birth weight, n(%) | 4 (13.33) | 6 (19.35) | 0.731 |
| Cesarean delivery, n(%) | 14 (46.67) | 13 (41.94) | 0.710 |
| Early postpartum hemorrhage, n(%) | 0 (0) | 1 (3.23) | >0.999 |
| Peripartum infection, n(%) | 0 | 0 | |
| NICU[a] admission, n(%) | 3 (10) | 8 (25.81) | 0.108 |

**Note**: [a]Neonatal Intensive Care Unit.

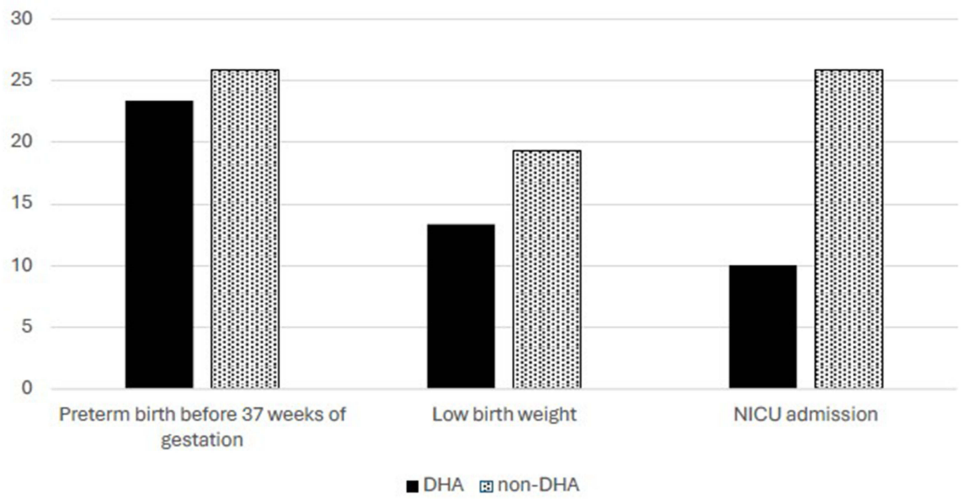


**Figure 2** Pregnancy and neonatal outcomes.

The mean birth weights were 2897 grams and 2890 grams in the DHA-treated and non-DHA-treated groups, respectively, with a p-value of 0.95. Figure 2. Although, the bar graph indicates that the group receiving DHA had a higher incidence of low-birth-weight infants who required care in the NICU. However, the rates of low-birth-weight neonates were 13.33% (4/30) and 19.35% (6/31) for the participant group receiving DHA and not receiving DHA, respectively, with a p-value of 0.73. The overall results did not show any statistically significant differences. In addition, the rates of cesarean sections, early postpartum hemorrhage, and NICU admissions did not exhibit any significant differences between the two groups, with corresponding p-values of 0.71, 0.99, and 0.1, respectively. After participating in the research, no subjects were found to have experienced side effects from DHA supplements.

## Discussion

Our study found that taking DHA supplements after a diagnosis of threatened preterm pregnancy does not reduce the actual rate of preterm birth for either early or late preterm births. However, In the DHA supplementation group, no pregnant women experienced early postpartum hemorrhage, and the rate of NICU admissions was lower compared to the non-DHA group. In comparison to the DHA supplement group, the group not receiving DHA exhibited a higher incidence of low birth weight infants, resulting in increased NICU admissions for hypoglycemia observation. Nevertheless, no statistically significant differences were observed in these outcomes. A 2018 Cochrane review analyzed 70 randomized controlled trials (RCTs) that included 19,927 women at varying levels of risk for poor pregnancy outcomes, comparing omega-3 long-chain polyunsaturated fatty acid (LCPUFA) interventions to a placebo or no omega-3.[12] This study found that DHA supplementation during pregnancy reduces the risk of preterm birth before 37 weeks of gestation, with rates of 13.4% in the control group compared to 11.9% in the DHA group. The risk ratio (RR) was 0.89, with a 95% confidence interval (CI) of 0.81 to 0.97, based on data from 26 randomized controlled trials (RCTs) involving 10,304 participants, providing high-quality evidence. Additionally, DHA supplementation was associated with a decreased risk of preterm birth before 34 weeks of gestation, showing rates of 4.6% in the control group versus 2.7% in the DHA group. The RR for this outcome was 0.58, with a 95% CI of 0.44 to 0.77, drawn from 9 RCTs consisting of 5,204 participants, also yielding high-quality evidence. In 2021, the ADORE trial was a multicenter, double-blind study involving 1,100 pregnant women.[13] The trial found that a higher daily dose of DHA (1,000 milligrams) significantly reduced the rate of early preterm birth compared to a lower dose of 200 milligrams per day. Specifically, the early preterm birth rate was 1.7% (9 out of 540) in the higher dose group, compared to 2.4% (12 out of 492) in the lower dose group, with a p-value of 0.81. This benefit was particularly evident among participants with low DHA status at enrollment, where the early preterm birth rates were 2.0% (5 out of 249) for the higher dose compared to 4.1% (9 out of 219) for the lower dose, with a p-value of 0.93. Additionally, complications during pregnancy, such as infections of the amniotic sac, premature rupture of membranes, and upper

urinary tract infections, were reported. However, these complications were less frequent in the group receiving a lower dose of DHA (200 milligrams per day) compared to the other group, although the difference was not statistically significant.

The recent expert review in AJOG/MFM (2024) highlights the significance of Omega-3 fatty acids during pregnancy, specifically in reducing the risks of preterm and early preterm births. While it is feasible to integrate laboratory assessments of DHA status into existing clinical testing protocols, not all countries currently have the capability for routine evaluations. An alternative method involves assessing typical DHA intake, which could help identify pregnant individuals who might benefit from high-dose DHA supplementation to mitigate preterm birth risks. Notably, women averaging less than 150 milligrams of DHA daily showed positive outcomes when assigned to high-dose DHA (800 or 1000 milligrams), compared to those receiving a lower dosage of 200 milligrams.[14] The northeastern region of Thailand is landlocked. As a result, the author believes that the local population likely has lower natural sources of DHA. To address this, the author decided to supplement their diet with a high dose of DHA, specifically 1000 milligrams. The hypothesis about premature labor indicates that fetal T-cell activation could be a new trigger for preterm labor and birth in cases once thought to be idiopathic. It's believed that issues with maternal regulatory T cells (Tregs) can lead to preterm birth, likely due to reduced immunosuppressive activity, which increases effector T-cell responses. Homeostatic macrophages are vital for maintaining pregnancy and supporting fetal growth. Additionally, transferring M2-polarized homeostatic macrophages may significantly help prevent inflammation-related preterm births.[15]

A 2019 study found an association between preterm birth and its subtypes with eicosanoid enzymatic pathways and inflammatory markers, which are endogenous signaling molecules derived from lipids, peptides, and DNA. The majority of associations observed were related to spontaneous preterm birth. The adaptive elastic-net analysis identified 5-oxo-eicosatetraenoic acid, resolvin D1, 5.6-epoxy-eicosatrienoic acid, and 15-deoxy-12,14-prostaglandin J2 as the most predictive factors.[16] Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 (n-3) fatty acids predominantly found in oily fish and fish oil supplements. These essential fatty acids have been recognized for their capacity to modulate inflammation by inhibiting several key processes, including leukocyte chemotaxis, which is the directed movement of white blood cells to sites of inflammation. The expression of adhesion molecules facilitates the adherence of white blood cells to the endothelial lining of blood vessels. The interactions between leukocytes and endothelial cells are essential for the inflammatory response. The synthesis of eicosanoids, such as prostaglandins and leukotrienes, that are derived from the omega-6 fatty acid arachidonic acid. The production of inflammatory cytokines, which are critical signaling molecules in the immune response. The reactivity of T-helper 1 lymphocytes, a subset of immune cells involved in the adaptive immune response.[17] In summary, EPA and DHA play a vital role in the regulation of inflammatory processes within the body, highlighting their importance in promoting health and well-being. They also have a beneficial effect on maintaining pregnancy, which is believed to be related to both processes: inflammation and the immune system. When evaluating DHA on its own, a 2017 study on DHA found that it may reduce the inflammatory response stimulated by lipopolysaccharide (LPS) in bovine mammary epithelial cells (bMEC). This effect occurs by suppressing the activation of nuclear transcription factor kappa B (NF-κB), and the mechanism is partly dependent on the activation of proliferator-activated receptor gamma (PPARγ).[18]

Furthermore, a study found that both DHA and EPA decreased LPS-induced NF-kappaB/DNA binding in THP-1 macrophages by about 13% ($P \leq 0.03$). However, DHA was found to significantly decrease the expression of nuclear p65 in macrophages ($P \leq 0.05$) and to increase the expression of cytoplasmic IkappaBalpha ($P \leq 0.05$).[19] The safety of DHA consumption is supported by research indicating that human milk, which is rich in DHA, provides approximately 315 milligrams per day for infants aged 1 to 6 months. This level of intake is considered safe. In studies of DHA supplementation for adults, doses varied from under 1 gram to 7.5 grams daily. These studies showed no consistent negative effects on key health markers like platelet function, lipid levels, or immune response. Thus, DHA is safe for both infants and adults. Recommended intake levels for DHA could mirror those found in human milk, which may reach amounts similar to those studied in adults.[20] No upper limit has been set regarding the intake of DHA and EPA during pregnancy, which would be potentially harmful. The United States Food and Drug Administration (FDA) has determined that a combined intake of DHA and EPA up to 3 grams per day, whether from diet or dietary supplements, is safe for consumers.[21] Our study found that taking 1000 milligrams of DHA daily had no side effects or risks. Research indicates that starting DHA supplements during preterm labor—regardless of whether there are changes in the cervix—does not

reduce the likelihood of premature birth. This suggests that if premature labor is already occurring, an inflammatory process is probably underway. It appears that administering DHA as a preventive measure may be more effective than trying to treat the condition once it has started. Individuals with a history of recurrent preterm birth are more likely to have a low pre-pregnancy weight, defined as being below 100 pounds, with a body mass index of less than 19.8 $kg/m^2$. This might suggest inadequate nutrition.[22] The risk of recurrent preterm birth is significantly heightened, with estimates ranging from 1.5 to 4 times or more, contingent upon the specific population. This risk escalates with each additional prior preterm birth and diminishes gestational age.[23] However, there was no difference in the history of premature births among the participants in this research. The limitation of our study is that we did not perform laboratory assessments to evaluate the DHA status of pregnant women experiencing threatened preterm labor. Furthermore, the reporting of participants' compliance remains reliant on self-reported data, which leads to inaccuracies. It is not clear whether participants in the control group consumed DHA from alternative sources, such as their diet or self-supplementation. The sample size of this study was insufficient to account for confounding variables. If a pregnant woman diagnosed with threatened preterm labor has low DHA levels, DHA supplementation may help reduce the rate of premature birth. Future research must prioritize the collection of comprehensive data on participants' DHA status to enable targeted interventions. Additionally, conducting studies within larger populations will aid in identifying confounding factors that may affect research outcomes.

## Conclusions

Taking DHA supplements after a diagnosis of threatened preterm pregnancy does not decrease the actual rates of early or late preterm births. To reduce the risk of premature birth, DHA should be taken from the beginning of pregnancy, with a recommendation to start in the first trimester. Numerous guidelines exist concerning DHA supplementation for individuals who are pregnant. However, the recent expert review in AJOG/MFM (2024) highlights the significance of Omega-3 fatty acids during pregnancy, suggested that individuals who are pregnant and have low DHA intake aim for about 600 to 1,000 milligrams per day of DHA and EPA or DHA alone. This should ideally start in the second trimester, no later than around 20 weeks of gestation, and should continue until childbirth or approximately 37 weeks of gestation.[14]

## Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

## Ethics

This study protocol was approved by the Center for Ethics in Human Research, Khon Kaen University: HE661462 and Khon Kaen Hospital Clinical Research Division: KEF67005. The study results will be published in a peer-reviewed journal and shared with stakeholders and participants. This protocol is submitted before the analysis of the results. After analysis and publication, data of this study will be available from the corresponding author upon reasonable request. This trial will comply with the Declaration of Helsinki.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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