INGREDIENTS
Doctor’s Best Prenatal Essential with Choline & DHA features five nutrients important for healthy pregnancy that may be difficult to get from diet alone: Choline (VitaCholine®), Folate (Quatrefolic®), Vitamin B12, Iron (Ferrochel®) and DHA (Docosahexaenoic Acid Omega-3). Prenatal Essentials with Choline & DHA also includes folate, which offers the biologically-active form of folic acid. Folate and folic acid have been shown to support healthy pregnancy in multiple human clinical trials. Methylcobalamin, is the more biologically-active form of Vitamin B-12. It also includes a high-quality form of Iron, ferrous bisglycinate chelate. Our DHA, which is shown to support healthy pregnancy, is from a vegetarian source of Omega-3, algae of Schizochytrium sp.

BENEFITS
Supports
• A healthy prenatal regimen*
• Healthy fetal and neural development during pregnancy*
• Breastfeeding moms for baby’s continued brain development*

Choline plays a major role in providing healthy methylation*
Methylation is one of the body’s most important and most common chemical processes, occurring in hundreds of essential chemical reactions. Many people have compromised methylation, which can cause or contribute to almost all health conditions.

For example, methylation:
• prevents some genetic diseases
• is the primary method of removing toxins in phase 2 liver detoxification
• is important for neurotransmitter synthesis and utilization
• is involved in balancing hormones
• is involved in converting homocysteine, which is dangerous in excess, back into methionine, an essential amino acid

The Role of Choline in Healthy Pregnancy*
Choline, a micronutrient found in food, plays a key role in healthy fetal development, particularly healthy brain development. The National Institute of Health established an Adequate Intake level of 425 mg/day for women, with upward adjustments to 450 and 550 mg/day during pregnancy and lactation, respectively. The importance of choline is supported by observations that a human fetus receives a large supply of choline during gestation; pregnancy depletes choline pools; human neonates are born with blood levels three times higher than maternal blood concentrations; and large amounts of choline are present in human milk. Central nervous system development is particularly sensitive to choline availability. Data show the majority of pregnant (and presumably lactating) women are not achieving target intake levels and common genetic variants may increase choline requirements beyond recommendations. Because choline is not in most prenatal vitamins (or multivitamins), choline supplementation may be needed to meet high pre- and postnatal demands for choline.*

A growing body of research supports choline as an essential nutrient during early development with life-long effects on memory and attentional processes. A review describes effects of alterations in dietary choline availability both in adulthood and during early development. Although modest effects of choline on cognitive processes have been reported when choline is administered to adult animals, the perinatal period is a critical time for cholinergic organization of brain function. Choline supplementation during this period increases memory capacity and precision of young adults and appears to prevent age-related memory and attentional decline. Deprivation of choline during early development

Supplement Facts
Serving: 4 Veggie Softgels
Serving Size: 1 Softgel

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Amount Per Serving</th>
<th>% Daily Value for Pregnant &amp; Lactating Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate (as (6S)-5-methyltetrafolinic acid, glucosamine salt)/(Quatrefolic®)</td>
<td>600 mcg DFE</td>
<td>100%</td>
</tr>
<tr>
<td>Vitamin B12 (as methylcobalamin)</td>
<td>2.8 mcg</td>
<td>100%</td>
</tr>
<tr>
<td>Choline (as choline L (+) bitartrate)(VitaCholine®)</td>
<td>550 mg</td>
<td>100%</td>
</tr>
<tr>
<td>Iron (as ferrous bisglycinate chelate)(Ferrochel®)</td>
<td>27 mg</td>
<td>100%</td>
</tr>
<tr>
<td>DHA (Docosahexaenoic Acid) (from algal oil (Schizochytrium sp.))</td>
<td>250 mg</td>
<td>†</td>
</tr>
</tbody>
</table>

† Daily Value not established.

Other Ingredients: Vegetarian softgel (food starch-modified, carrageenan, sorbitol, glycerin, purified water, red iron oxide, black iron oxide), sunflower oil, yellow beeswax, sunflower lecithin.

Suggested Adult Use: Take 4 softgels with food or as directed by a nutritionally informed physician.

WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

Non-GMO / Gluten Free / Soy Free / Vegetarian
Store in a cool dry place.

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
leads to compromised cognitive function and increased decline with age. The authors conclude that choline availability may be related to relatively permanent alterations in cholinergic synapse function, which they call ‘metabolic imprinting’.\(^2\)

One study examined the impact of choline metabolism in a long-term, randomized, controlled feeding trial among pregnant, lactating, and nonpregnant (NP) women consuming 480 or 930 mg/d choline and meeting folate-intake recommendations. Gene variants impairing folate metabolism, influenced choline dynamics, frequently through interactions with reproductive state and choline intake. Women with these variants partitioned more dietary choline toward phosphatidylcholine (PC) biosynthesis via the cytidine diphosphate (CDP)-choline pathway at the expense of betaine synthesis even when use of betaine as a methyl donor was increased. Choline intakes of 930 mg/d restored partitioning of dietary choline between betaine and CDP-PC among NP and lactating women with risk genotypes. Overall, the findings indicate that loss-of-function variants in folate-metabolizing enzymes strain cellular PC production, possibly via impaired folate-dependent phosphatidylethanolamine-N-methyltransferase (PEMT)-PC synthesis and suggest that women with these risk genotypes may benefit from choline intakes exceeding current recommendations.\(^3\)

Another study used stable isotope methodology to examine the effects of pregnancy on choline partitioning and the metabolic activity of choline-related pathways. Healthy third-trimester pregnant (n = 26; initially week 27 of gestation) and nonpregnant (n = 21) women consumed 22% of their total choline intake (480 or 930 mg/d) as methyl-d9-choline for the final 6 wk of a 12-wk feeding study. The enhanced use of choline for phosphatidylcholine (PC) production shows the substantial demand in the human body for choline during late pregnancy and may imply a unique requirement of choline by the developing fetus.\(^4\)

A separate study tested whether choline intake affects indicators of choline-related lipid metabolism, including erythrocyte and plasma phosphatidylcholine (PC)-docosahexaenoic acid (DHA) and PC: phosphatidylethanolamine (PE) ratios, in pregnant women in the third trimester and nonpregnant women. Pregnant (n = 26) and nonpregnant (n = 21) women consumed 480 or 930 mg choline/d and a daily DHA supplement for 12 wk. Blood was collected at baseline and at the midpoint and end of the study. PC-DHA was analyzed as the proportion of total PC fatty acids. The researchers concluded that a higher choline intake may increase phosphatidylethanolamine (PE) N-methyltransferase (PEMT) activity, resulting in greater PC-DHA enrichment of the PC molecule in nonpregnant women. Increased production of PC-DHA during pregnancy indicates elevated PEMT activity and a higher demand for methyl donors such as choline to facilitate metabolism during pregnancy.\(^5\) Researchers investigated the effects of perinatal choline supplementation on the development of cerebral inhibition in human infants.

A randomized placebo-controlled clinical trial of dietary phosphatidylcholine supplementation was conducted with 100 healthy pregnant women, starting in the second trimester. Supplementation to twice normal dietary levels for mother or newborn continued through the third postnatal month. Infants’ electrophysiological recordings of inhibition of the P50 component of the cerebral evoked response to paired sounds were analyzed. The criterion for inhibition was suppression of the amplitude of the second P50 response by at least half, compared with the first response. Neonatal developmental delay in inhibition is associated with attentional problems as the child matures. The researchers found that perinatal choline activates timely development of cerebral inhibition, even in the presence of gene mutations that otherwise delay it. Thus, choline supplementation during pregnancy may help reduce risk of attentional problems in children.\(^6\)

A study investigated the influence of maternal choline intake on the human placental transcriptome, with a special interest in its role in modulating placental vascular function. Healthy pregnant women (n=26, wk 26-29 gestation) were randomized to 480 mg choline/d, an intake level approximating the adequate intake of 450 mg/d, or 930 mg/d for 12 wk. Maternal blood and placental samples were retrieved at delivery. Whole genome expression microarrays were used to identify placental genes and biological processes impacted by maternal choline intake. Maternal choline intake influenced a wide array of genes (n=166) and biological processes (n=197), including those related to vascular function. Of special interest was the 30% down-regulation of the antiangiogenic factor and preeclampsia risk marker frms-like tyrosine kinase-1 (sFLT1) in the placenta tissues obtained from the 930 vs. 480 mg/d choline intake group. Similar decreases were detected in maternal blood sFLT1 protein concentrations. The down-regulation of sFLT1 by choline treatment was confirmed in a human trophoblast cell culture model and may be related to enhanced acetylcholine signaling. These findings indicate that supplementing the maternal diet with extra choline may improve placentation angiogenesis and mitigate some of the pathological antecedents of preeclampsia.\(^7\)

As an extension of the previous 12-wk dose-response choline feeding study, researchers investigated the effect of maternal choline intake (930 vs. 480 mg/d) on the epigenetic state of cortisol-regulating genes, and their expression, in placenta and cord venous blood. The higher maternal choline intake yielded higher placental promoter methylation of the cortisol-regulating genes, corticotropin releasing hormone and glucocorticoid receptor; lower placental CRH transcript abundance; lower cord blood leukocyte promoter methylation of CRH and NR3C1; and 33% lower cord plasma cortisol. In addition, placental global DNA methylation and dimethylated histone H3 at lysine 9 (H3K9me2) were higher in the 930 mg choline/d group, as was the expression of select placental methyltransferases. The in-utero availability of methyl donors, such as choline, may modify fetal epigenetic marks and lead to sustainable functional alterations throughout the life course. These data suggest that maternal choline intake in humans modulates the epigenetic state of genes that regulate fetal HPA axis reactivity as well as the epigenomic status of fetal derived tissues.\(^8\)

Other researchers quantified the effects of pregnancy and maternal choline intake on maternal and fetal indicators of choline metabolism. Healthy pregnant (n = 26; 27 wk gestation) and nonpregnant (n = 21) women were randomly assigned to receive 480 or 930 mg choline/d for 12 wk. Fasting blood samples and placental tissue and umbilical cord venous blood were collected and analyzed for choline and its metabolites. These data suggest that an increment of 25 mg choline/d to meet the demands of pregnancy is insufficient and show that a higher maternal choline intake increases the use of choline as a methyl donor in both maternal and fetal compartments.\(^9\)

Another study attempted to determine whether total choline intake and/or SNPs influence concentrations of choline and its metabolites in human breast milk and plasma. Researchers gave a total of 103 pregnant women supplemental choline or a placebo from 18 wk gestation to 45 d postpartum and genotyped the women for 370 common SNPs. At 45 d postpartum, they measured choline metabolite concentrations in breast milk and plasma and assessed the dietary intake of choline by using a 3-d food record. The study found that total intake of choline and genotype can influence the concentrations of choline and its metabolites in the breast milk and blood of lactating women and thereby affect the amount of choline available to the developing infant.\(^10\)

An analysis of 34 rodent studies linked choline availability during gestation and perinatal development to offspring neurological function or performance in cognitive and behavioral tests. The evidence suggests choline supplementation during development improves offspring performance on cognitive or behavioral tests, and improves a variety of neurological functional indicators: (1) enhanced performance was observed.

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
The authors conclude that choline is an important component of memory function in the aged is, in part, determined by mother's choline. Mothers had extra choline even when these animals are elderly. Thus, lifelong memory enhancement. This memory function enhancement or during the second week of life), their brain function changes, resulting in prenatal stress and cognitive effects of prenatal alcohol exposure in offspring. The likely mechanism for these choline effects involves DNA methylation, altered gene expression, and associated changes in stem cell proliferation and differentiation.\textsuperscript{12}

Studies with animal models indicate the prenatal choline availability influences neural and cognitive development. Specifically, prenatal choline supplementation has been shown to enhance working memory and hippocampal long-term potentiation (LTP) in adult offspring. However, the cellular mechanisms underlying these effects remain unclear. This study reports that choline supplementation during a 6-day gestational period results in greater excitatory responsiveness, reduced hyperpolarizations (sAHPs), enhanced depolarizing potentials (ADPs), larger somata, and greater basal dendritic arborization among hippocampal CA1 pyramidal cells studied postnatally in juvenile rats (20–25 days of age). The researchers conclude that dietary supplementation with choline during a brief, critical, period of prenatal development alters the structure and function of hippocampal pyramidal cells.\textsuperscript{13}

Choline is a dietary component essential for normal function of all cells. In 1998 the National Academy of Sciences, USA, issued a report identifying choline as a required nutrient for humans and recommended daily intake amounts. Ongoing studies are finding that men have a higher requirement than do postmenopausal women, who in turn need more than premenopausal women. Notably, pregnancy and lactation can deplete maternal reserves of choline. Meanwhile, choline is critical for normal brain development. When rat pups receive choline supplements (in utero or during the second week of life), their brain function changes, resulting in lifelong memory enhancement. This memory function enhancement appears to be due to memory center (hippocampus) changes. These changes are so important that investigators can pick out animals whose mothers had extra choline even when these animals are elderly. Thus, memory function in the aged is, in part, determined by mother's choline levels. The authors conclude that choline is an important component of diet, especially during pregnancy.\textsuperscript{14}

Another study examined effects of supplemental choline given prenatally to pregnant rats and postnatally (tubed into rat pup stomachs) on memory function and neurochemical measures of brain cholinergic activity of male albino rats when they became adults. The data demonstrate that perinatal choline supplementation causes (a) long-term facilitative effects on working and reference memory components of a 12-arm radial maze task, and (b) alterations of muscarinic receptor density as indexed by [3H] quinuclidinyl benzilate (QNB) binding and choline acetyltransferase (ChAT) levels in the hippocampus and frontal cortex of adult rats. The researchers conclude that these brain changes are highly correlated with improved memory function and reduced working and reference memory errors.\textsuperscript{15}

Another study supplemented male albino rats with choline both prenatally (in pregnant rats' diet) and postnatally (subcutaneous injections). At age 60 days rats were tested on a 12- and 18-arm radial maze task. Results indicate that, compared to control littermates, perinatal choline-treated rats show more accurate performance on both working and reference memory. This performance difference was apparent on the first block of sessions and continued throughout training. The researchers concluded that the difference between choline and control rats is due to long-term enhancement of spatial memory capacity and precision.\textsuperscript{16}

**Folate is Important for Healthy Pregnancy**

In a secondary analysis of data from a double-blind randomized controlled trial, researchers assessed the effect of prenatal supplementation with multiple micronutrients (MMN) or iron + folic acid (IFA), versus folic acid (FA) alone, on risk of spontaneous preterm birth (SPB) and the impact of supplementation timing on SPB. A total of 18,775 nulliparous pregnant women enrolled between 2006 and 2009 were randomly assigned to receive daily FA, IFA, or MMN from the period before 20 weeks' gestation to delivery. Starting use of FA, IFA, or MMN supplements before the 12th week of gestation produced a 41%-45% reduction in risk of SPB. The authors concluded that early prenatal enrollment and micronutrient use, including folic acid and iron, during the first trimester of pregnancy appeared to be of importance for SPB risk reduction.\textsuperscript{17}

A randomized clinical trial assessed the effect of low and high doses of folic acid on homocysteine (Hcy) levels, blood pressure, urea, creatinine and neonatal outcome. Elevated Hcy levels may be associated with some fetal abnormalities and potential blood flow problems in the placenta. A randomized clinical trial was done from April 2008 to March 2013. Four-hundred and sixty nulliparous pregnant women were randomly assigned into two groups. Group 1 (n = 230) received 0.5 mg of folic acid and group 2 (n = 230) received 5 mg of folic acid per daily. They were followed until delivery. Blood pressure and laboratory changes, including plasma Hcy levels, were measured and compared between the groups. The study concluded that a high dose of folic acid supplements throughout pregnancy reduces Hcy concentrations at delivery.\textsuperscript{18}

Another study analyzed the long-term effects of fish oil (FO), 5-methyltetrahydrofolate (5-MTHF), or FO+5-MTHF prenatal supplementation on attention networks. Participants were 136 children randomly assigned to receive FO and/or 5-MTHF or placebo prenatal supplementation, recalled for a new examination 8.5 y later. The response conflict-resolution ability (using congruent and incongruent conditions), alerting, and spatial orienting of attention were evaluated with behavioral measures (Attention Network Test), electroencephalography/event-related potentials (ERPs), and standardized low-resolution brain electromagnetic tomography (sLORETA). The study concluded that folate supplementation during pregnancy improves children's ability to solve response conflicts. This advantage seems to be based on higher activation of the midcingulate cortex, indicating that early nutrition influences the functionality of specific brain areas involved in executive functions.\textsuperscript{19}

Other researchers assessed the association between cumulative micronutrient intake (CMI) and fetal growth by secondary analysis of a randomized controlled trial of iron and folic acid supplements with 1056 pregnant females. The researchers concluded that the effect of iron and folic acid supplementation on fetal growth is cumulative. The supplementation should therefore begin as early as possible in pregnancy, even if the growth increment per CMI is higher in late than in early pregnancy. The researchers also noted that women with a low body mass index (BMI) also experienced extra energy from supplementation.\textsuperscript{20}

A separate study examined the risk of birth defects in relation to diabetes mellitus and the lack of use of periconceptional vitamins or supplements that contain folic acid. The National Birth Defects Prevention Study

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
Vitamin B-12 Role in Healthy Pregnancy*

A randomized, partially open-labeled intervention trial examined the effect of supplemental high-quality protein and vitamin B-12 on third-trimester methionine kinetics. Pregnant women with low serum vitamin B-12 concentrations (~200 pmol/L) were randomly assigned to 1 of 3 groups: the first group received balanced protein-energy supplementation of 500 mL milk/d plus a 10-µg vitamin B-12 tablet/d (M+B-12 group; n = 30), the second group received milk (500 mL/d) plus a placebo tablet (M+P group; n = 30), and the third group received a placebo tablet alone (P group; n = 33).

Third-trimester fasting plasma amino acid kinetics were measured. Placental mRNA expression of genes involved in methionine pathways, placental long interspersed nuclear elements 1 (LINE-1) methylation, and promoter methylation levels of vascular endothelial growth factor (VEGF) were analyzed. The study concluded that combined vitamin B-12 and balanced protein-energy supplementation increased the homocysteine remethylation rate in late pregnancy. Thus, vitamin B-12 along with balanced protein-energy supplementation is critical for optimal functioning of the methionine cycle in the third trimester of pregnancy in these women with low serum vitamin B-12 in early pregnancy.27

Another study sought to quantify the effects of pregnancy and lactation on the vitamin B-12 status response to a known and highly controlled vitamin B-12 intake. As part of a 10-12 wk feeding trial, pregnant (26–29 wk gestation; n = 26), lactating (5 wk postpartum; n = 28), and control (nonpregnant, nonlactating; n = 21) women consumed vitamin B-12 amounts of ~8.6 µg/d [mixed diet (~6 µg/d) plus a prenatal multivitamin supplement (2.6 µg/d)]. Serum vitamin B-12, holotranscobalamin (bioactive form of vitamin B-12), methylmalonic acid (MMA), and homocysteine were measured at baseline and study-end. The study concluded that pregnancy and lactation alter vitamin B-12 status in a manner consistent with enhanced vitamin B-12 supply to the child. Consumption of the study vitamin B-12 dose (~3 times the RDA) increased the bioactive form of vitamin B-12, suggesting that women in these reproductive states may benefit from vitamin B-12 intakes exceeding current recommendations.28

Other researchers evaluated whether daily oral vitamin B-12 supplementation during pregnancy increases maternal and infant measures of vitamin B-12 status. The researchers performed a randomized, placebo-controlled clinical trial. Pregnant women <14 wk of gestation in Bangalore, India, were randomly assigned to receive daily oral supplementation with vitamin B-12 (50 µg) or placebo through 6 wk postpartum. All women were administered iron and folic acid supplements throughout pregnancy. One hundred eighty-three women were randomly assigned to receive vitamin B-12 and 183 to receive placebo. Compared with placebo recipients, vitamin B-12-supplemented women had significantly higher plasma vitamin B-12 concentrations at both the second and third trimesters. At 6 wk postpartum, median breast milk vitamin B-12 concentration was 136 pmol/L in vitamin B-12-supplemented women vs. 87 pmol/L in placebo group. Among vitamin B-12-supplemented women, the incidence of delivering an infant with intrauterine growth retardation was 33 of 131 (25%) vs. 43 of 125 (34%) in placebo. In a subset of infants tested at 6 wk of age, median plasma vitamin B-12 concentration was 199 pmol/L in those born to supplemented women vs. 139 pmol/L in the placebo group. Infant plasma methylmalonic acid and homocysteine concentrations were significantly lower in the vitamin B-12 group as well. The researchers concluded that oral supplementation of urban Indian women with vitamin B-12 throughout pregnancy and early lactation significantly increases vitamin B-12 status of mothers and infants.29

Another study examined the association between maternal folate and vitamin B-12 status in pregnancy on offspring insulin resistance and examine whether the effects of maternal micronutrient supplementation varied by baseline maternal folate and/or vitamin B-12 status. Pregnant women were cluster randomized to receive daily supplements containing vitamin A alone or with folic acid, folic acid + iron, folic acid + iron + zinc, or a multiple micronutrient. In a subsample (n = 1132), micronutrient status biomarkers were analyzed at baseline and late pregnancy. Children born to the women who participated in the trial were visited at 6–8 y of age. Fasting plasma glucose and insulin were used to estimate insulin resistance using

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
Iron Important for Healthy Pregnancy *

Researchers compared the effects of iron-folic acid (IFA) or multiple micronutrients (MMN) with folic acid (FA) supplements on birth weight among pregnant women with mild/no anemia or high Hb levels. A double-blind randomised controlled trial was conducted with 18,775 pregnant women with mild/no anemia (145 g/l) baseline Hb levels, in 2006-2009. The researchers concluded that iron supplements improved birth weight in women with very high Hb levels before 20 weeks of gestation.1

Another study assessed effects of prenatal iron-folate supplementation on maternal and neonatal iron status. Enrollment occurred June 2009 through December 2011. Women with uncomplicated single pregnancies at ≤20 wk gestation, aged ≥18 y, and with hemoglobin ≥100 g/L were randomly assigned 1:1 to receive daily iron (300 mg ferrous sulphate) or placebo + 0.4 mg folate from enrollment to birth. Iron status was assessed in maternal venous blood (at enrollment and at or near term) and cord blood. Primary outcomes were as follows: 1) maternal iron deficiency (ID) defined in 2 ways as serum ferritin (SF) <15 µg/L and body iron (BI) <0 mg/kg; 2) maternal ID anemia [ID + anemia (IDA); hemoglobin <110 g/L]; and 3) neonatal ID (cord blood ferritin <75 µg/L or zinc protoporphyrin/heme >118 µmol/mol). The study concluded that prenatal iron supplementation reduced anemia, ID, and IDA in pregnant women in rural China, but most women and >45% of neonates had ID, regardless of supplementation.32

A separate study examined the efficacy of pre-pregnancy supplementation with iron and multivitamins to reduce the prevalence of anemia during the periconceptional period among non-pregnant females age 15–29 years (n = 802). A double-blind, randomized controlled trial was conducted in which participants were randomized to receive daily oral supplements of folic acid alone, folic acid and iron, or folic acid, iron, and vitamins A, B-complex, C, and E at approximately single recommended dietary allowance (RDA) doses for six months. The study concluded that daily oral supplementation with iron and folic acid among women and adolescents prior to pregnancy reduces risk of anemia.33

A study investigated changes in hematological status, oxidative stress and erythrocyte membrane fluidity in anemic pregnant women after Fe supplementation with and without combined vitamins. The study was a 2-month double-blind, randomized trial. Pregnant women (n 164) were allocated to four groups: group C was the placebo control group; group I was supplemented daily with 60 mg Fe (ferrous sulphate) daily; group IF was supplemented daily with Fe plus 400 µg folic acid; group IM was supplemented daily with Fe plus 2 mg retinol and 1 mg riboflavin, respectively. The findings show that supplementation with Fe and particularly in combination with vitamins could improve the hematological status as well as oxidative stress and erythrocyte membrane fluidity.34

Another study assessed effects of iron supplementation in infancy and/or pregnancy on infant iron status, illnesses, and growth at 9 months. Infants born to women in a pregnancy iron supplementation trial were randomly assigned 1:1 to iron [–1 mg Fe/kg · d] or placebo from 6 wk to 9 months. Excluding infants with cord ferritin <35 µg/L. Study groups were pregnancy placebo/infancy placebo (placebo/placebo), pregnancy placebo/infancy iron (placebo/iron), pregnancy iron/infancy placebo (iron/placebo), and pregnancy iron/infancy iron (iron/iron). The primary outcome was 9-mo iron status: iron deficiency (ID) by cutoff ≤2 abnormal iron measures) or body iron <0 mg/kg and ID + anemia (hemoglobin <110 g/L). Secondary outcomes were doctor visits or hospitalizations and weight or length gain from birth to 9 mo. Iron supplementation in Chinese infants reduced ID at 9 months without adverse effects on growth or illness. Effects of iron supplementation in pregnancy were observed only when higher amounts of iron were distributed in infancy, suggesting the importance of mothers supplementing with iron during breastfeeding.35

Other researchers measured the effect of antenatal iron supplementation on maternal Plasmodium infection risk, maternal iron status, and neonatal outcomes. In a randomized placebo-controlled trial among 470 women aged 15 to 45 years with singleton pregnancies, gestational age of 13 to 23 weeks, and hemoglobin concentration of 9 g/dL or greater. All women received 5.7 mg iron/day through flour fortification and supervised daily supplementation with 60 mg of elemental iron (as ferrous fumarate, n = 237 women) or placebo (n = 233) from randomization until 1 month postpartum. The researchers found that administration of daily iron supplementation, compared with administration of placebo, led to increased birth weight.36

Another study attempted to determine the impact of iron deficiency anemia (IDA) in pregnancy on young child development. The study was a 2-year follow-up of 850 children born to women who participated in a double-blind cluster randomized controlled trial of prenatal micronutrient supplementation. The women were randomly assigned to receive either daily folic acid, iron/folic acid (60 mg iron), or multiple micronutrients (with 30 mg iron) during pregnancy. Children were categorized into the prenatal-IDA and prenatal-non–IDA groups based on the mother’s hemoglobin in the third trimester. Each group contained 3 subgroups based on mother’s treatment: folic acid, iron/folic acid, and multiple micronutrients. Bayley scales of infant development were administered to the children to assess their development at 3, 6, 12, 18, and 24 months of age. The study concluded that prenatal IDA in the third trimester negatively affects mental development of the child. However, prenatal supplementation with sufficient iron protects child development even when the woman’s IDA was not properly corrected in pregnancy.37

DHA for Healthy Pregnancy*

Researchers assessed the effects of maternal DHA supplementation on neurological development of children. Healthy pregnant women from Spain, Germany, and Hungary were randomly assigned to a dietary supplement consisting of either fish oil (FO) (500 mg/d DHA + 150 mg/d EPA), 400 µg/d 5-methyltetrahydrofolate, both, or placebo from wk 20 of gestation until delivery. Fatty acids in plasma and erythrocyte phospholipids (PL) were determined in maternal blood at gestational week 20 and 30 and in cord and maternal blood at delivery. Neurological development was assessed with the Hempel examination at the age of 4 y and the Touwen examination at 5.5 y. The researchers concluded that higher DHA levels in cord blood may be related to a better neurological outcome at 5.5 y of age.38

A study aimed to assess the effect of n-3 fatty acid supplementation in pregnancy on offspring specialized pro-resolving mediator (SPM) at birth and 12 years of age (12 years). In all, ninety-eight atopic pregnant women were randomised to 3.7 g daily n-3 fatty acids or a control (olive oil), from 20 weeks gestation until delivery. Blood was collected from the offspring at birth and at 12 years. Plasma SPM consisting of 18-hydroxyecosapentaenoic acid (18-HEPE), E-series resolvins, 17-hydroxydocosahexaenoic acid (17-HDHA), D-series resolvins, 14-hydroxydocosahexaenoic acid (14-HDHA), 10 S,17S-dihydroxydocosahexaenoic acid, maresins and protectin 1, were measured by liquid chromatography-tandem MS. The study found that n-3 Fatty acid supplementation during pregnancy was associated with an increase in SPM precursors in the offspring at birth. The presence of these SPM, particularly at birth, may have functions relevant in the newborn that remain to be established, which may be useful for future investigations.39

Another study randomized women to 600 mg/d DHA or a placebo for the last two trimesters of pregnancy. Infants of these mothers were then followed on tests of visual habitation at 4, 6, and 9 months of age. Infants of DHA supplemented mothers maintained high levels of sustained...
attention (SA) across the first year while SA declined for the placebo group. The supplemented group also showed significantly reduced attrition on habituation tasks, especially at 6 and 9 mo. The findings support the suggestion that prenatal DHA may positively affect infants’ attention and regulation of state.  

Other researchers evaluated global cognition, behavior, and attention at age 5 y in the offspring of women who participated in a randomized controlled trial of prenatal DHA supplementation. A total of 1094 woman were randomly assigned to receive 400 mg of either DHA or placebo/d from 18 to 22 wk of pregnancy until delivery. They assessed cognitive development and behavioral and executive functioning, including attention, in 797 offspring at age 5 y (82% of 973 live births) using McCarthy Scales of Children’s Abilities (MSCA), the parental scale of the Behavioral Assessment System for Children, Second Edition (BASC-2), and the Conners’ Kiddie Continuous Performance Test (K-CPT). The researchers concluded that prenatal exposure to DHA may contribute to improved sustained attention in preschool children.

Another study tested the effectiveness of prenatal docosahexaenoic acid (DHA) supplementation on birth outcomes and infant development. The Nutrition and Pregnancy Study (NAPS) is a double-blind, randomized controlled trial of prenatal DHA supplementation. Sixty-four pregnant, African American women were enrolled at 16–21 weeks of gestation and randomized to either 450mg/day of DHA (22:6n-3) (n=43) or soybean placebo (n=21). Complete data were obtained for 49 infants (76.5%) at 3-month assessment. Supplementation with DHA or placebo continued from beginning of enrollment through delivery. Data on birth outcomes were collected from medical records. At 3 months postpartum, mothers brought infants to the laboratory where the Bayley Scales of Infant Development (BSID-III) were administered and cortisol response to the Face-to-Face Still-Face (FFSF) paradigm was assessed. Infants of women living in urban, low-income environments who received DHA supplementation had more optimal birth outcomes and more modulated cortisol response to a stressor. DHA supplementation may be effective in attenuating the negative effects of prenatal stress on offspring development.

Other researchers explored the role of Omega-3 fatty acids as modulators of oxidative stress, especially during gestation and postnatal life. One hundred ten pregnant women were divided in two groups: control group CT (400 mL/day of the control dairy drink); supplemented group FO (400 mL/day of the fish oil-enriched dairy drink (±400-mg EPA-DHA/day)). Different biomarkers of oxidative damage were determined in the mothers at enrollment, at delivery and at 2.5 and 4 months postpartum and newborns at delivery and at 2.5 months postpartum. The supplementation prevents oxidative stress in the mother and neonate during the first months of postnatal life, being a potential nutritional strategy to prevent functional alterations associated with oxidative stress that have important repercussions for neonate development in early postnatal life.

Another study compared DHA supplementation to nutrition education to increase DHA consumption from fish and DHA fortified foods. This two-part intervention included a randomized double-blind placebo controlled DHA supplementation arm and a nutrition education arm designed to increase intake of DHA from dietary sources by 300 mg per day. 871 pregnant women aged 18-40 were recruited between 16 and 20 weeks of gestation of whom 564 completed the study and complete delivery data was available in 505 women and infants. Subjects received either 300 or 600 mg DHA or olive oil placebo, or nutrition education. Gestational length. The study concluded that nutrition education or supplementation with DHA can be effective in increasing gestational length.

Other researchers conducted a double-blind, randomized, placebo-controlled trial. They randomly assigned 1,094 pregnant women (18-35 years of age) to receive 400 mg/d of algal docosahexaenoic acid (DHA) or placebo from 18 to 22 weeks of gestation through delivery. Birth outcomes and respiratory symptoms information until 18 months were available for 869 mother–child pairs. Questionnaires were administered, and maternal blood samples were obtained at baseline. Maternal atopy was based on specific IgE levels. During follow-up, information on infants’ respiratory symptoms was collected through questionnaires administered at 1, 3, 6, 9, 12, and 18 months of age. Negative binomial regression models were used to evaluate the effect of supplementation on respiratory symptoms in infants. The results support the hypothesis that DHA supplementation during pregnancy may decrease incidence of respiratory symptoms in children with a history of maternal atopy.

A separate study sought to test whether prenatal dietary supplementation with ω-3 PUFA during pregnancy may modulate infant immune system epigenetics. This study was based on a randomized intervention trial conducted in pregnant women supplemented daily with 400 mg docosahexaenoic acid (DHA) or a placebo from 18 to 22 wk of gestation to parturition. They applied quantitative profiling of DNA methylation states (n = 261). The results indicate that maternal supplementation with ω-3 PUFA during pregnancy may modulate global methylation levels and the Th1/Th2 balance in infants. Therefore, epigenetic mechanisms could provide attractive targets for prenatal modulation and prevention of inflammatory disorders and potentially other related diseases in childhood and adulthood.

In a Phase III, double-blind, randomized controlled trial, 350 women consumed capsules containing 600mg DHA/day or placebo in the last half of gestation. The DHA group resulted in greater gestation duration (reduction in early preterm) and greater infant size (reduction of very-low birth weight). The DHA group had shorter hospital stays for infants born preterm than the placebo group.

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
**SCIENTIFIC REFERENCES**


*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.*