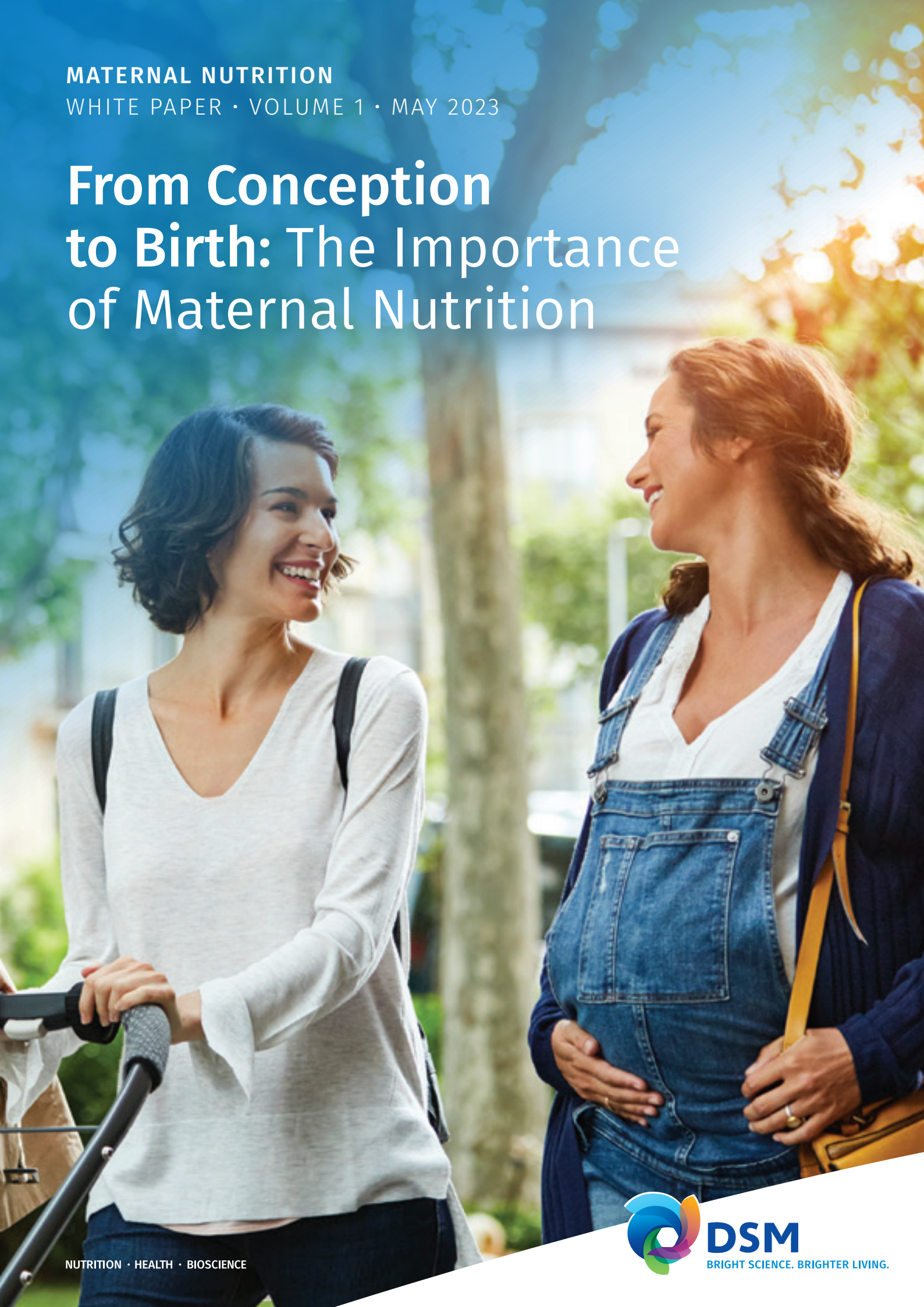
MATERNAL NUTRITION

WHITE PAPER · VOLUME 1 · MAY 2023

From Conception to Birth: The Importance of Maternal Nutrition



NUTRITION · HEALTH · BIOSCIENCE

DSM

BRIGHT SCIENCE. BRIGHTER LIVING.

Table of Contents

1 | Executive Summary

Maternal nutrition refers to the nutrient intake and dietary habits of women from the time they start trying to conceive through pregnancy, the postpartum period, and lactation. The importance of maternal nutrition cannot be overstated, as adequate nutrition during the prenatal stage and pregnancy is essential to ensure healthy fetal growth and development, as well as the mother's health during and after pregnancy. This window of opportunity represents a vulnerable and impactful period of time, when the nutrients provided have lasting impacts to both mom and baby. Reflecting this, in 2020, the WHO released updated antenatal care recommendations for a positive pregnancy experience. Their new guidelines give explicit recommendations that pregnant women should consume a multiple micronutrient supplement – which includes 15 vitamins and minerals – during pregnancy, replacing their previous advice for iron and folic acid supplements alone.

As rates of infertility continue to rise, research is growing on how modifiable lifestyle factors, like diet and nutrient intake, impact fertility outcomes. An evidence base is emerging for the relationship between dietary supplements and fertility outcomes, particularly in women utilizing assisted reproduction. While some dietary patterns such as high sugar and saturated fat intake are noted to hinder fertility, the beneficial effects of folate, unsaturated fats like n-3 fatty acids, and vitamin D, and consistent intake of fruit, vegetables, and fish have been documented. Research is also emerging on links between other nutrients such as co-enzyme Q10, cobalamin, and inositol and fertility.

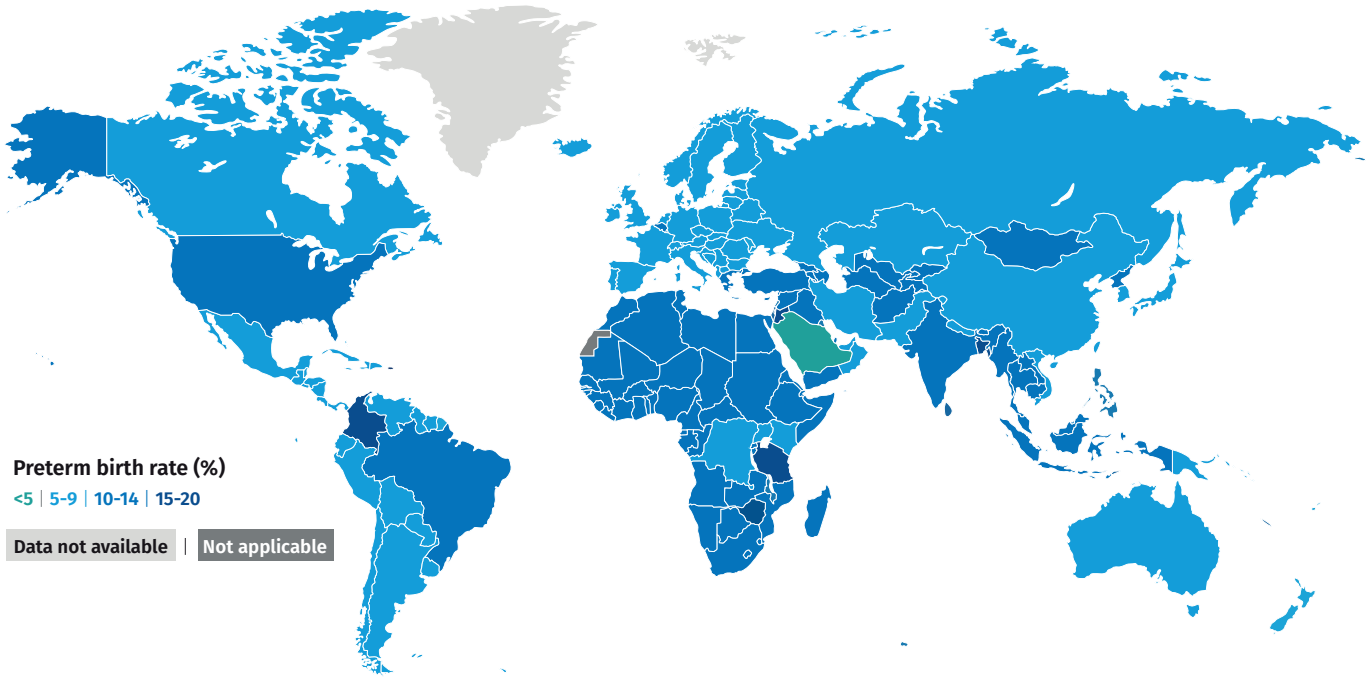
Scientific data have highlighted the importance of certain nutrients when it comes to prenatal and pregnancy outcomes: iron, as iron deficiency is the most common micronutrient deficiency known to impact maternal health and infant outcomes; folate, for its role in preventing neural tube defects; DHA, for its ability to reduce the risk of preterm delivery and support infant brain and eye health; vitamin D for its association with reducing the incidence of miscarriage and pre-eclampsia; choline, for the critical role it plays in early brain development; and carotenoids – with a focus on lutein and zeaxanthin – as research has illustrated an association between carotenoids and visual and cognitive health. The literature around these nutrients enhances our knowledge of just how fundamental they are in supporting maternal and infant health, as well as in shaping the health of future generations.

2 | Recent Advances in Maternal Nutrition

The nutrition and care that mothers and babies receive during the first 1,000 days - from conception until the child's 2nd birthday - have an immense impact on long-term growth and development.

The perinatal period is a critical window of time where optimal nutrition supports fertility, fetal growth and development, and the mother's health throughout conception, pregnancy, and the post-partum period.[1] However, measures of maternal and reproductive wellness are less than encouraging. Global fertility rates – the total number of births in a year per 1,000 women of reproductive age – have decreased dramatically, falling roughly 50% in the last 50 years. There are many reasons for this, including women's empowerment in the workforce, lower child mortality, and the increased cost of raising children.[2] However, infertility contributes to this trend, with available data suggesting that 1 in 6 people will experience infertility in their lifetime.[3] Preterm birth remains a crucial public health challenge, with global rates of premature birth estimated to be greater than 10%,[4] and complications from early birth are the most common cause of mortality in children less than 5 years of age.[5] Additionally, preterm birth disproportionately impacts infants of racial and ethnic minorities.[6] Finally, maternal morbidity, which includes the short- or long-term consequences of labor and delivery that negatively impact a woman's health, has been steadily increasing in recent years.[7]

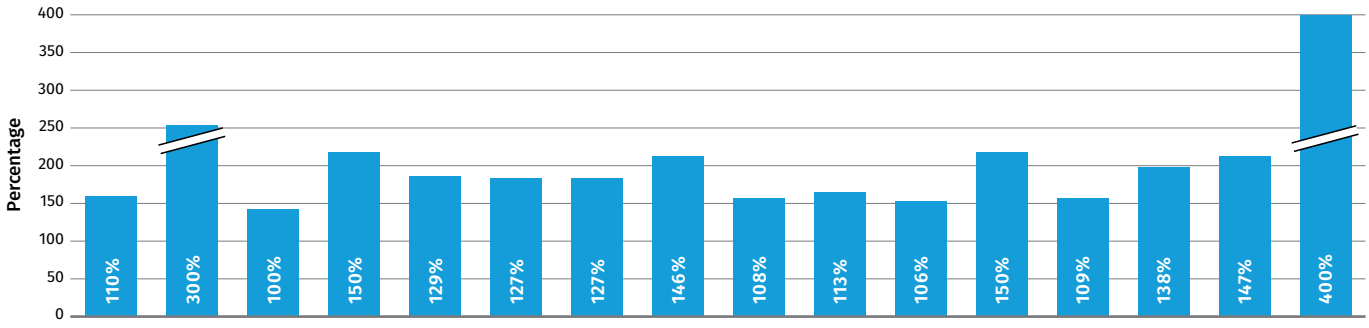
Figure 1: **Estimated preterm birth rates in 2014. U.S. rates reflect 2023 data from the Centers for Disease Control and Prevention (CDC)**[4,8]



Throughout life, nutrient requirements differ according to gender and life stage. But women have distinct nutrient needs before, during, and after pregnancy. Optimizing the nutrition status of the mother ultimately supports the growth, development, and health outcomes of her infant.[1,9] **Figure 2** illustrates these increased requirements. Further detail on recommended daily nutrient intakes during pregnancy by authoritative bodies can be found in the Appendix, **Table A1**.

As the body of evidence surrounding the impact of nutrient intakes on fertility and pregnancy outcomes evolves, so do expert recommendations. A noteworthy example is the recent update to the World Health Organization (WHO) guideline for micronutrient supplementation during pregnancy.

Figure 2: **Micronutrient needs during pregnancy compared to baseline requirements (non-pregnant 19-50 year olds)** [9,10]



	Vit A	Vit D	Vit E	Folate	Niacin	Riboflavin	Thiamin	Vit B6	Vit B12	Vit C	Choline	Iron	Selenium	Zinc	Iodine	Omega-3s
Pregnant RDA	770 mcg	15 mcg	15 mcg	600 mcg	18 mg	1.4 mg	1.4 mg	1.9 mg	2.6 mcg	85 mg	450 mg	27 mg	60 mcg	11 mg	220 mcg	Up to 1,000 mg*
Baseline RDA	700 mcg	5 mcg	15 mcg	400m cg	14 mg	1.1 mg	1.1 mg	1.3 mg	2.4 mcg	75 mg	42 mg	18 mg	55 mcg	8 mg	150 mcg	250 mg

* Not an RDA. 1,000 mg recommended for pregnant women with low intake. **RDA**: Recommended Dietary Allowance

2.1. A Historic Update to the World Health Organization Recommendations

In 2020, the WHO released updated guidelines on antenatal care recommendations for a positive pregnancy experience. Their ***Nutritional Interventions Update: Multiple micronutrient supplements during pregnancy*** guidelines give explicit recommendations that pregnant women should consume a multiple micronutrient supplement (MMS) – which includes 15 vitamins and minerals – during pregnancy.[11] These recent guidelines replace the WHO's 2016 recommendations on antenatal care for a positive pregnancy experience, which focused primarily on iron and folic acid supplementation during pregnancy.

The newest WHO antenatal care guidelines were derived from evidence in randomized controlled trials, an independent participant meta-analysis, and a Cochrane systematic review establishing that MMS provide a greater benefit than only iron and folic acid supplements in reducing the risk of adverse pregnancy outcomes.[11-14] Supplementation timing is also of importance: initiation of MMS earlier than 20 weeks gestation had a greater impact on reducing the risk of preterm birth compared to later initiation of MMS (risk ratio [RR] 0.89, 95% confidence interval [CI] 0.85-0.93, *P*=0.03).[12] A recent Cochrane Review – also considered in the WHO's updated guidance – provided evidence that a daily, multiple micronutrient supplement containing iron and folic acid, vs. iron and folic acid supplements alone, significantly reduced the risk for low birth weight (LBW) (average RR 0.88, 95% CI 0.85-0.91) and small for gestational age (SGA) (average RR 0.92, 95% CI 0.88-0.97) in low- and middle-income countries (LMICs).[14] Some outcome benefits for MMS are illustrated in **Figure 3**.

The new recommended formulation – the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) – has been widely tested in clinical trials from various geographical regions. These studies provide evidence that the UNIMMAP prevents iron-deficiency anemia as effectively as iron and folic acid supplementation alone and additionally reduces the risk of having a LBW infant (*P*<0.049) or an infant born SGA (*P*<0.03).[12,18] **Figure 4** provides the complete list of nutrients included in the UNIMMAP.

Figure 3: Benefits of MMS Compared to IFAS Alone[11,12,15-17]

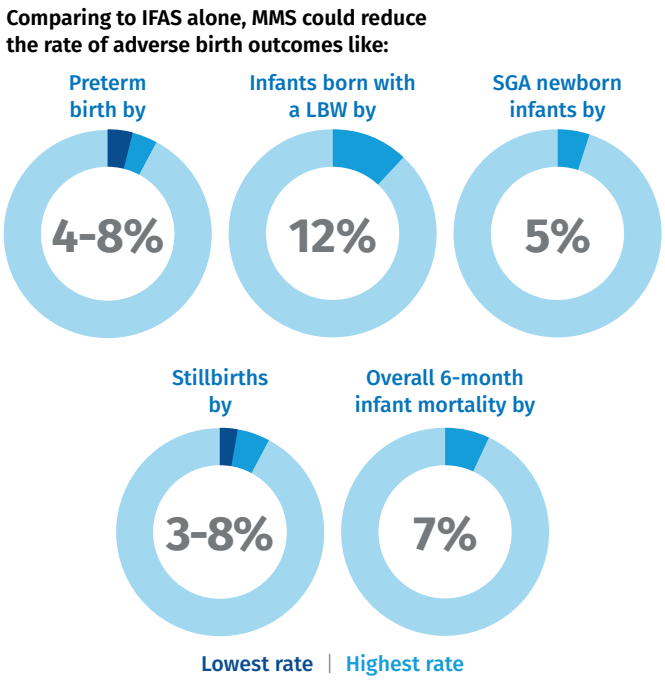
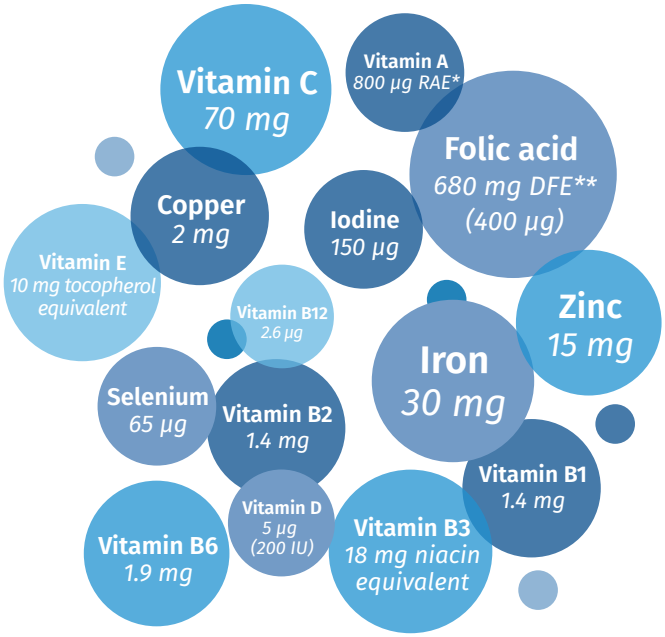


Figure 4: **Vitamins and Minerals Included in the UNIMMAP Formulation with Recommended Intakes**[11]



***RAE:** Retinol Activity Equivalent; ****DFE:** dietary folate equivalent; **UNIMMAP:** United Nations International Multiple Micronutrient Antenatal Preparation
IFAS: Iron Folic Acid Supplementation; **MMS:** Multiple Micronutrient Supplements; **LBW:** low birth weight; **SGA:** small for gestational age.

2.2. Nutrient Intake and Female Fertility: A Growing Body of Evidence

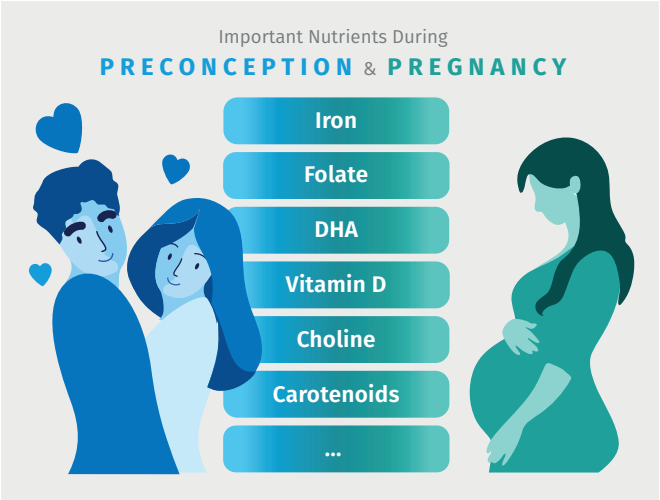
Infertility is a growing clinical and public health concern. It is estimated that 15-25% of women in western countries struggle with infertility, and worldwide, it affects up to 48 million couples and 186 million individuals.[19,20] Infertility is defined by the inability to become or remain pregnant after at least 12 months of trying to conceive. It can be caused by anatomical abnormalities of the reproductive system, diminished ovarian reserve, and hormonal disorders, but the cause is often unexplained.[21]

Many of these women turn to assisted reproduction technologies (ART) such as *in-vitro* fertilization (IVF). The advent of ART has facilitated the targeted study of how modifiable lifestyle factors – such as diet and nutrient intake – impact fertility outcomes. These outcomes can be measured in several ways: the number of follicles that mature, the number of oocytes retrieved, the number of high-grade embryos developed, and implantation success.[22] A body of literature is emerging on the relationship between dietary supplement intake and fertility outcomes, especially in women undergoing assisted reproduction.[19,23]

2.3. Maternal Nutrition is Central to Infant and Child Development

While ample clinical studies and observational trials have demonstrated the influential role of nutrition overall in pregnancy outcomes – for both mother and baby[12,14,24] – select nutrients are of particular importance and will be highlighted in this review. These include: iron, as iron deficiency is the most common micronutrient deficiency known to impact maternal health and infant outcomes[25-27]; folate, for its role in preventing neural tube defects (NTDs) and encouraging optimal cognitive outcomes[28,29]; docosahexaenoic acid (DHA), for its ability to reduce the risk of preterm delivery and support infant brain and eye health[25,30,31]; vitamin D, for its association in reducing the incidence of miscarriage and pre-eclampsia and supporting bone formation[32,33]; choline, for the critical role it plays in early brain development[25,34,35]; and finally, carotenoids with a focus on lutein and zeaxanthin, as research has illustrated an association between these carotenoids and visual and cognitive health.[36,37]

Figure 5: **Nutrients of focus during the prenatal and pregnancy stages**



3 | Key Nutrients for Supporting Maternal and Infant Health Outcomes

According to current scientific knowledge, several nutrients play a key role in certain aspects of infant development or in supporting the health and well-being of a woman on the motherhood journey. For some nutrients, the importance and relevance overlaps throughout more than one stage of the perinatal time frame; others are critical during a distinct phase of development. Here, we will explore these key nutrients – iron, folate, DHA, vitamin D, choline, and carotenoids – and their positions in supporting maternal and infant health.

3.1. The Role of Iron in Female Fertility & Pregnancy

Iron Overview

Iron is an essential element that plays critical roles throughout periconception and pregnancy.[38,39] Dietary sources of iron include meats, liver, fish, shellfish, fortified grains, vegetables, nuts, legumes, and dietary supplements.[40]

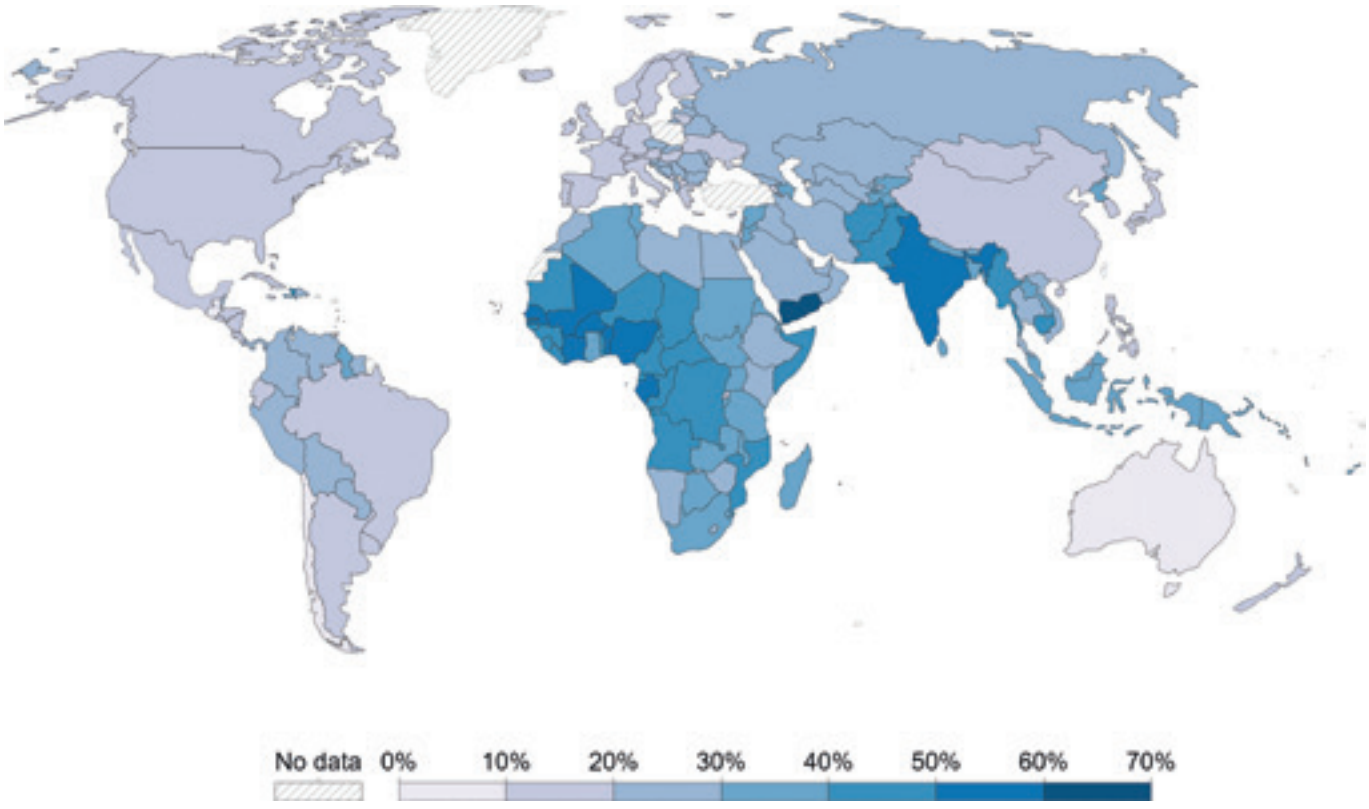
Iron is essential for the function of all cells. It is a component in hundreds of proteins and enzymes that support essential biological functions. It is a crucial element of red blood cells (RBC) and in oxygen transport.[38] Oxygen – fundamental for all living cells – is carried throughout the body by hemoglobin, a protein in RBCs, and iron is pivotal in making hemoglobin. Thus, iron is needed to carry oxygen to visceral cells where it can be used for cellular metabolism and energy production.[38] Iron is also an indispensable cofactor for several enzymes involved in DNA synthesis and repair, which is critical for oocyte maturation and healthy fetal development.[38,41-44] Adequate iron intake during pregnancy is also crucial to build iron stores in the fetus. Human milk is low in iron, and exclusively breastfed infants rely on the iron stores they are born with for the first 6 months of life.[45]

Iron Deficiency

When iron deficiency (ID; indicated by low ferritin) progresses to iron deficiency anemia (IDA; indicated by low hemoglobin), hemoglobin levels, and thus, arterial oxygen levels decrease, resulting in symptoms such as shortness of breath and fatigue.[38,46] IDA is a global public health issue that impacts both resource-limited and resource-rich countries.[38] Globally, an estimated 36% of pregnant women and 30% of women of childbearing age have IDA.[47,48] Rates vary according to a country's socioeconomic status; among pregnant women and women of childbearing age, rates range from ~13% and 15%, respectively, in high-income countries to ~49% to 52%, respectively, in West and Central Africa.[47,48] Women of childbearing age are prone to ID and IDA due to iron losses during menstrual bleeding and increased iron requirements during pregnancy.[39,49] **Figure 6** highlights the global prevalence of anemia in women of reproductive age.

Deficiency of iron is a common cause of IDA, but other nutrients are also involved in iron metabolism: vitamin C, vitamin A, and riboflavin help with iron absorption; vitamin E, vitamin C, and riboflavin are involved in iron mobilization; and vitamin A, vitamin B6, vitamin B12, folic acid, and riboflavin are involved in RBC synthesis.[50] Additionally, there is some evidence to support a role of vitamin D in anemia reduction, most likely through vitamin D's anti-inflammatory role as a regulator of hepcidin, allowing iron export from ferroportin, increasing serum iron, and making iron available for erythropoiesis.[51]

Figure 6: **Prevalence of anemia in women of reproductive age (ages 15-49), measured as the percentage of women with a hemoglobin level less than 110 gm/L at sea level**[52]



Iron and Female Fertility

ID and IDA may impact female fertility.[53,54] Women with a history of recurrent pregnancy loss have lower ferritin levels and are more likely to have ID compared to women without fertility issues. Ferritin levels are also negatively correlated with the number of pregnancy losses.[53] Unfortunately, little is known about how IDA impacts follicular development, ovulation, and the menstrual cycle in humans.[55]

The Impact of Iron Supplementation on Female Fertility

In a large prospective cohort study, women of childbearing age who took iron supplements were 40% less likely to develop ovulatory infertility compared to those who did not, suggesting a protective effect of iron supplementation (RR=0.60, 95% CI 0.39-0.92).[54] Another prospective cohort study found some evidence linking iron supplement use with improved fecundability rate (the monthly probability of conception), especially for women with risk factors for IDA.[56] Randomized controlled trials are needed to determine if iron supplementation improves fertility outcomes in women trying to conceive, especially among those with IDA.[54,56]

Iron and Pregnancy Outcomes

IDA is associated with negative pregnancy outcomes such as intrauterine growth restriction, preterm labor, stillbirth, LBW, and neonatal anemia. Anemia is also associated with SGA, low Apgar score, and perinatal and neonatal death. Women with anemia have a high risk of maternal morbidities such as spontaneous abortions, antepartum hemorrhage, postpartum hemorrhage, preeclampsia, and prolonged labor.[58] When iron levels are inadequate during pregnancy, DNA methylation increases, which alters gene expression and can impact offspring health. Such alterations in DNA can be hereditary and may even impact future generations.[41,59]

Both IDA and excess iron during pregnancy have been associated with negative neurodevelopmental outcomes in offspring.[60] Some pregnant women are susceptible to iron overload, including those with replete iron stores who take excess iron supplements and women with genetic mutations in the HFE gene (involved in iron metabolism), which increases intestinal iron absorption. Although the need for iron supplementation to prevent IDA during pregnancy is well-known, tailored supplementation according to hemoglobin levels may be ideal.[61]

The Impact of Iron Supplementation on Pregnancy Outcomes

A 2015 Cochrane review comparing daily oral iron supplementation to no iron or a placebo included 44 trials of 43,274 women.[62] The authors concluded that daily iron supplementation reduced ID at term by 57% (RR 0.43; 95% CI 0.27-0.66, low-quality evidence) and IDA at term by 67% (RR 0.33; 95% CI 0.16-0.69). Women taking daily iron were more likely to have higher hemoglobin concentrations at term and postpartum, but were also at increased risk of having hemoglobin concentrations above 130g/L during pregnancy and at term, although there was high heterogeneity for this outcome and a wide range of doses were used in the included studies. There were no differences in maternal infection, maternal mortality, neonatal death, or congenital abnormalities between groups.[62]

Another Cochrane review compared daily iron supplementation with intermittent iron supplementation during pregnancy.[63] The review included data from 21 trials and 5,490 women. Maternal and infant outcomes were similar in both groups, but the intermittent iron group had fewer side effects and a decreased risk of high hemoglobin levels, though the risk of mild anemia at term was increased. The authors concluded that intermittent iron supplementation may be a suitable alternative for pregnant women who are not anemic.[63]

Alternatives to Oral Iron Supplementation

There are alternatives to oral iron supplementation for preventing and treating IDA in pregnant women. Oral iron is inexpensive and easy to use, but there can be side effects including nausea and constipation, already common in pregnancy.[38,64] Intravenous iron has been shown to be as effective as oral iron, but is typically reserved for women with severe IDA later in pregnancy, those who do not tolerate oral iron, or in cases where oral iron is not increasing blood markers of IDA.[38] Another less common alternative is lactoferrin, which is an iron binding protein naturally found in mammalian milks.[64] Lactoferrin improves iron status by increasing dietary iron absorption from the intestine. Bovine lactoferrin (100 mg twice daily) has been shown in multiple clinical trials to improve hemoglobin and ferritin levels in pregnant females without the untoward side effects of other iron forms. Lactoferrin may also have additional benefits such as reducing inflammation, protecting against pathogens, and regulating immune system activity.[64]

Iron Supplementation Recommendations for Pregnant Women

Recommendations for iron supplementation during pregnancy differ by region. The Centers for Disease Control and Prevention (CDC) and WHO recommend routine iron supplementation during pregnancy, but the American Congress of Obstetricians and Gynecologists (ACOG), the European Food Safety Authority (EFSA), and the Australian Department of Health (ADH) only recommend supplementation in women at risk or those identified as having IDA.[65-69]

Table 1: **Iron Supplementation Recommendations for Pregnant Women**

Organization	Iron Supplement Recommendations
American College of Obstetricians and Gynecologists[65]	Screen all pregnant women for IDA and provide an iron supplement in addition to a prenatal vitamin to those with IDA.
United States Centers for Disease Control[66]	Supplement all pregnant women with low dose iron (30 mg/day) and screen for IDA. Women with IDA should supplement with 60-120 mg/day of iron.
European Food Safety Authority[68]	Supplement if at risk of IDA.
Australia Department of Health[69]	Advise iron supplementation to pregnant women based on their hemoglobin concentration at 28 weeks. Advise pregnant women taking an iron supplement that weekly supplementation (80-300 mg elemental iron) is as effective as daily supplementation (30-60 mg elemental iron) in preventing (but not treating) iron-deficiency anemia, with fewer adverse effects.
World Health Organization[11]	Supplement with a multiple micronutrient supplement including 30 mg of iron.

3.2. The Role of Folate (Vitamin B9) in Female Fertility and Pregnancy

Folate Overview

Folate is an essential vitamin widely recognized for its importance before and during pregnancy. Folate occurs naturally as methylfolate in fruits, vegetables, and legumes. Folic acid is the synthetic and less bioavailable form of folate found in fortified grains and dietary supplements.[70] As a methyl-donor and co-enzyme in the synthesis of DNA and RNA, folate is central to the modulation of gene expression. It is required for proper cell division and normal embryo and fetal development. During pregnancy, folate is essential for protein metabolism and is known to play a critical role in neural tube development.[71,72] Early folic acid supplementation has been a global public health initiative considering the abundance of evidence for its ability to prevent neural tube disorders, as well as megaloblastic anemia.[25,71] Mandatory folic acid fortification of staple foods began in the U.S. in 1998 and is currently implemented in ~60 countries. Countries that adopted mandatory fortification programs saw significant declines in NTDs and maintain rates of NTDs that are lower than countries with either voluntary or no fortification programs.[73] Initiatives continue to expand mandatory folic acid fortification globally.[73,74]

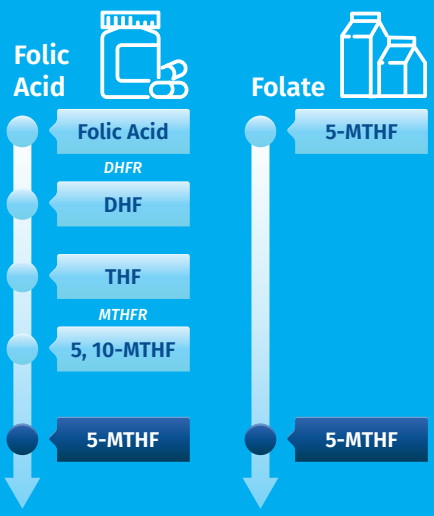
Folate Deficiency

Despite global public health initiatives to increase folate consumption through folic acid fortification and targeted supplementation, inadequate intakes remain common.[75] Folate deficiency can impair RBC synthesis, leading to megaloblastic anemia. This is characterized by reduced and abnormal RBC production and symptoms similar to IDA.[72,75]

Folate deficiency also leads to high homocysteine levels.[76] Homocysteine is an amino acid known as a marker of inflammation, and elevated levels are associated with a myriad of health issues including cardiovascular disease and cancer. Adequate intakes of folate, vitamin B6, and vitamin B12 are necessary to maintain healthy homocysteine levels.[76] Among women of childbearing age, folate deficiency is estimated to occur in <5% of women in higher income countries, but this increases to >20% in lower income countries.[75] However, even folate insufficiency can increase a woman's risk of having a baby with NTDs.[72,75] When it comes to NTD prevention, time is of the essence. RBC folate levels should be adequate before the neural tube closes between 4 and 6 weeks of pregnancy. A RBC threshold of >906 Nmol/L has been established as the benchmark for protection against NTDs.[77] It has been estimated that folate insufficiency (<906 Nmol/L) occurs in >40% of women of childbearing age in most of the countries with available data; this includes developed nations.[75]

Some women are more susceptible to folate insufficiency and deficiency because they carry polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene.[78] MTHFR is the enzyme needed to convert folic acid, the synthetic form in fortified foods and supplements, into the active form, methylfolate, found naturally in foods and RBCs.[79] The occurrence of MTHFR polymorphisms varies, but approximately one-third of the general population are heterozygous carriers.[78,80] MTHFR polymorphisms can impair enzyme activity by 30-70%, resulting in reduced RBC folate status.[78,8]

Figure 7: **Folate metabolism and genetic polymorphisms**[82-87]



Folate and Female Fertility

In both men and women, the MTHFR polymorphism is associated with infertility and failed ART cycles, which may be directly linked to folate status.[78,88] In a prospective cohort study of 116,480 female nurses of childbearing age, those with pre-pregnancy folate intakes in the highest quartile (>851 µg/day) had a 9% reduced risk of spontaneous abortion compared to those in the lowest quartile of intake (<285 µg/day) (RR 0.91, 95% CI 0.82-1.02).[88] Although the exact pathophysiology is unclear, it has been hypothesized that the reduced availability of methylfolate leads to DNA hypomethylation and thus, poor embryo development and early pregnancy loss in women.[78]

Folate Supplementation and Female Fertility

Research suggests that folate supplementation can positively impact female fertility, with possible mechanisms related to its impact on ovarian function, implantation, and embryogenesis.[89] In the same prospective cohort study mentioned above, women who were supplementing with >730 µg/day of folic acid before pregnancy had a 20% reduced risk of spontaneous abortion compared to those not taking a supplement (RR 0.80, 95% CI 0.71-0.90), suggesting that folic acid supplementation may protect against early fetal demise.[88] In a large randomized controlled trial (n=7,905), women randomized to a supplement with 800 µg folic acid were more likely to conceive, and conceived earlier, than those receiving a placebo (71.3% vs. 67.9%, *P*=0.001).[19,90] In a smaller trial, 93 women who had been unable to conceive for 6 to 36 months were randomized to a supplement with 400 µg of folic acid or a placebo for 3 months. Those in the supplement group were more likely to conceive than those receiving a placebo (26% vs. 10%, *P*=0.01).[91] In an observational study, folic acid supplementation during IVF encouraged a higher number of total oocytes and mature oocytes compared to no supplementation.[92] However, folic acid supplementation does not appear to improve outcomes for women with unexplained infertility undergoing IVF.[93]

Women with MTHFR gene polymorphisms are at increased risk for infertility. In this population, providing supplemental folate as methylfolate rather than folic acid may be especially beneficial. Since methylfolate does not require enzymatic processing, its bioavailability is not impacted by the presence of MTHFR gene mutations.[94] In a retrospective study of 269 Italian women who underwent IVF, they received either 400 µg folic acid or 400 µg methylfolate along with 5 µg vitamin B12 and 3 mg vitamin B6 according to their physician's prescribing practices. A significantly higher percentage of women who received methylfolate had healthy fertilized eggs available for transplantation, clinically confirmed pregnancies, and live births compared to those who received folic acid. The women in the methylfolate group also had a greater number of mature oocytes available for fertilization. There was no difference in early pregnancy loss between the two groups. Although this is a retrospective study and not a robust randomized controlled trial, it does show promise that supplementation with methylfolate may support positive IVF outcomes.[94]

Adding to the evidence base for the potential benefits of methylfolate, a clinical trial of 100 women with a known MTHFR mutation and a history of at least 2 early pregnancy losses were randomized to receive either 5,000 µg folic acid or 1,000 µg methylfolate from the time of a positive pregnancy test until the end of the first trimester. Though a small trial, the results were dramatic: women in the MTHF group experienced 16% fewer miscarriages and 52% more full term births compared to those in the folic acid group.[95] While encouraging, larger randomized controlled trials are needed.

Folate and Pregnancy

The importance of folate for normal fetal development during pregnancy has been firmly established. It is well-known that inadequate folate levels are associated with NTDs.[71,96] Other folate-sensitive birth defects include oral facial cleft, congenital heart defects, spina bifida, and urinary tract anomalies. Inadequate folate status has also been correlated with preterm birth and infants born SGA.[71,96] Further, while the data available to date are inconclusive, emerging studies have shown associations between maternal folate levels that are either low or high and a greater risk of childhood autism or allergy.[97-100] These findings illustrate that maintaining a healthy range of folate levels is critical to neurological and immune system development. Finally, folate insufficiency has also been correlated with perinatal depression which effects ~15% of women, making it the most common complication of pregnancy.[101,102]

Folate Supplementation and Pregnancy Outcomes

Folic acid is the most clinically studied form of folate for supplementation during pregnancy, and the evidence around its efficacy in preventing NTDs serves as the foundation for expert recommendations for folate supplementation.[71,77,103,104]

Figure 8: **Overview of the characteristics and potential benefits of L-Methylfolate**[70-72,85,108]

Recent studies have demonstrated that methylfolate is as effective as folic acid in increasing plasma folate, an important metric when measuring effectiveness. In a 12-week study, women of childbearing age who were supplemented with methylfolate had higher RBC folate levels compared to those supplemented with an equimolar dose of folic acid, suggesting methylfolate may, in fact, be more effective than folic acid in raising blood folate levels in pregnant women.[105]

As stated above, achieving target blood folate levels (906 Nmol/L) before the neural tube closes between 4 and 6 weeks of pregnancy is critical for the prevention of NTDs.[77] Studies have shown that this protective threshold is reached after 8 weeks in women supplemented with the recommended dose of 400 µg folic acid.[106] In another small study, when the recommended dose of folic acid was combined with 451 µg methylfolate, the protective threshold was reached after only 4 weeks of supplementation.[107] While more robust study is needed, the findings to date begin to build an evidence base for the consideration of methylfolate as an addition or alternative to folic acid in prenatal supplements.

Folate Supplementation Recommendations for Women of Childbearing Age and Pregnant Women

Recommendations for folic acid supplementation during pregnancy are consistent globally. Due to the available evidence, folic acid is the form of folate recommended by the WHO and other expert bodies before and during pregnancy at a dose of 400 µg daily.[1,25,96,109]

Table 2: **Folic Acid Supplementation Recommendations for Women of Childbearing Age and Pregnant Women**

Organization	Folic Acid Supplement Recommendations
American College of Obstetricians and Gynecologists[110]	All women of childbearing age should supplement with 400 µg folic acid per day. Women with increased risk of NTDs should supplement with 4,000 µg/day.
United States Preventative Services Task Force[104]	Women who are planning or capable of pregnancy should take a daily supplement containing 400-800 µg folic acid.
Australia Department of Health[111]	Advise dietary supplementation of 400 µg per day folic acid, ideally from 1 month before conception and throughout the first 3 months of pregnancy to reduce the risk of NTDs.
World Health Organization[11]	Supplement with a multiple micronutrient supplement including 400 µg folic acid.

3.3. The Role of Docosahexaenoic Acid (DHA) in Female Fertility and Pregnancy

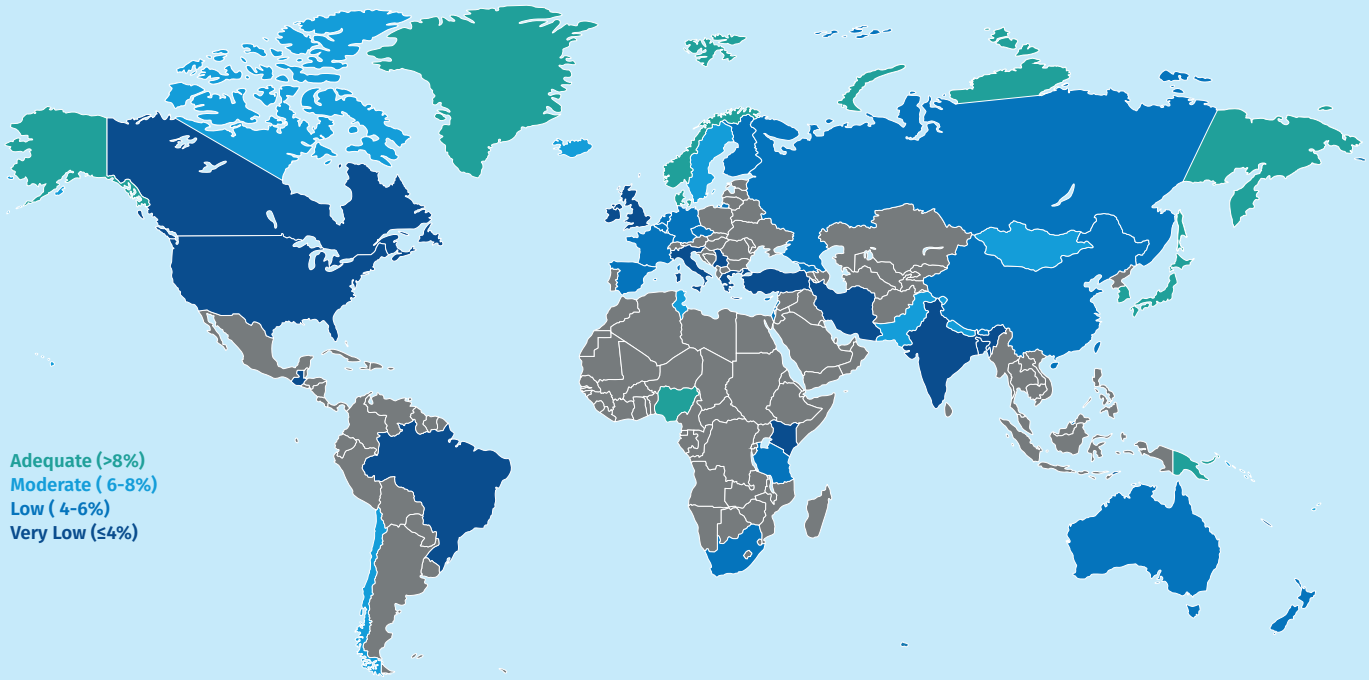
DHA Overview

Docosahexaenoic acid (DHA) is an omega-3 long-chain polyunsaturated fatty acid (LCPUFA) mainly found in seafood. More recently, DHA-rich eggs and DHA-fortified milks have become available. Both fish oil and algal-derived dietary supplements are also sources of DHA.[112] Some preclinical and emerging data from clinical trials suggest that a diet rich in omega-3 PUFAs has a positive impact on oocyte quality, embryo implantation, and reproductive hormones, illustrating the potential to positively impact fertility.[113] During pregnancy, DHA is intricately involved in the development of the brain and the immune system, and plays a central role in visual acuity.[1,114,115] DHA is the predominant omega-3 fatty acid in the brain and is critical for myelination and visual development.[116,117] Omega-3 fatty acids also play a role in a mother's mental health and wellbeing, with studies showing a link between maternal eicosapentaenoic acid (EPA) and DHA levels and perinatal depression.[118] Finally, an extensive body of evidence demonstrates an important role for DHA to positively support pregnancy duration and reduce the risk of premature birth.[119,120]

Inadequate DHA Intake

While DHA is not considered an essential nutrient as humans can synthesize it from the essential fatty acid alpha-linolenic acid, it is sometimes referred to as conditionally essential during pregnancy.[121,122] Due to genetic variations in enzyme activity, some people have a limited ability to synthesize DHA.[123] Still, DHA deficiency is not defined. However, low dietary DHA intakes and very low blood levels are widespread, with >96% of the global population having sub-optimal levels, as seen in **Figure 9**.[124] When DHA levels are reduced, it increases the ratio of omega-6 to omega-3 fatty acids, resulting in a predominance of pro-inflammatory omega-6 fatty acids. Alternatively, a higher omega-3 to omega-6 ratio favors anti-inflammatory pathways.[125] Although clinical criteria to diagnose a true DHA deficiency have not been identified, a low blood fatty acid status is associated with increased non-communicable disease risk.[124]

Figure 9: **Global blood levels of the sum of EPA+DHA. Values are percentages of omega-3 fatty acids (EPA + DHA) in erythrocyte equivalents**[124]



DHA and Female Fertility

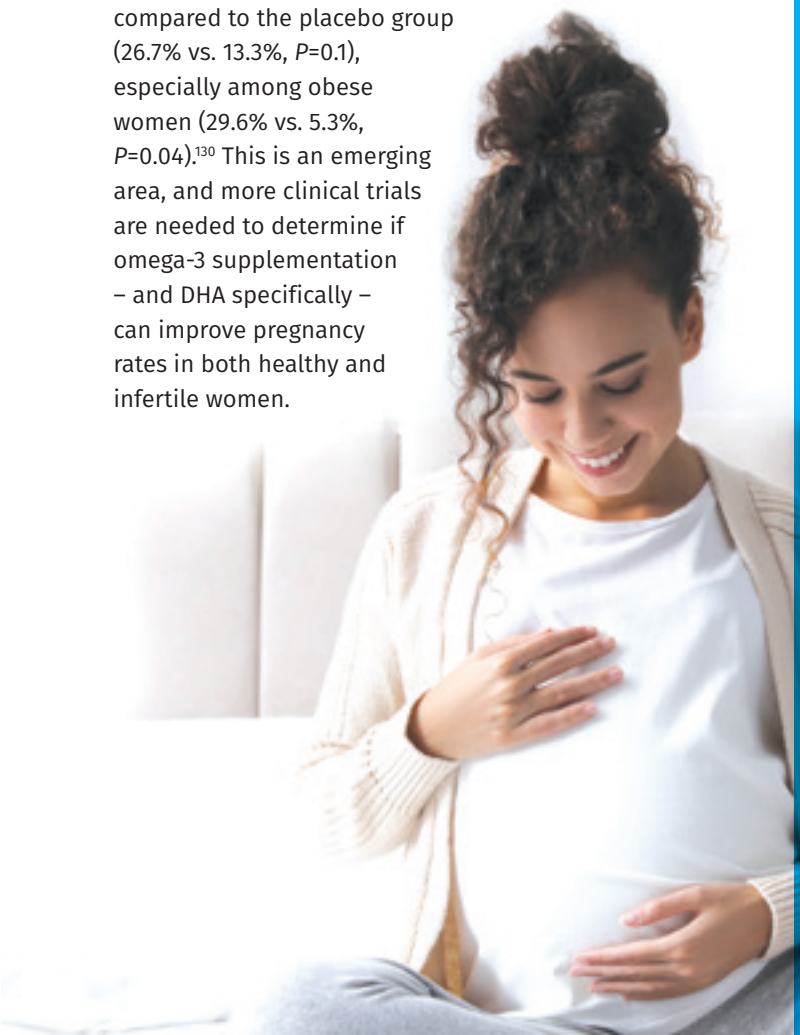
The overall quality of the maternal diet is known to impact fertility. Studies have shown that a Mediterranean-style diet focusing on seafood, lean animal protein, whole grains, fruits and vegetables is supportive of early pregnancy success.[19,23] One of the hallmarks of the Mediterranean diet is low saturated fat intake and a focus on heart-healthy unsaturated fats, including the omega-3 fatty acid DHA. In a study to evaluate the relationship between intakes of PUFAs and infertility in healthy women, omega-3 intake was only slightly associated with infertility, yet intakes in the highest tertile were shown to reduce the risk of infertility by nearly 40% when compared to intakes at the lowest tertile. Further, omega-3 fatty acid levels positively correlated with desirable ART outcomes.[126]

In a small randomized controlled trial (RCT) in women with overweight and obesity undergoing IVF, those who became pregnant had higher levels of PUFA intake (P=0.03), with a trend towards higher omega-3 PUFA intake (P=0.06).[127] Another analysis of 100 women undergoing ART revealed that higher serum levels of LCPUFAs were linked to a higher probability of a clinical pregnancy and live birth. Specifically, for every 1% increase in serum LCPUFA level, the probability of both clinical pregnancy and live birth increased by 8%. Additionally, replacing just 1% of energy from saturated fatty acids with omega-3 LCPUFAs resulted in a higher probability of a live birth, with a RR of 2.37 (95% CI 1.02, 5.51).[113] Researchers suspect that the proinflammatory aspects of omega-6 and the anti-inflammatory characteristics of omega-3 fatty acids underly the mechanisms for this proposed link. More study is needed in this area – in particular, on different types and ratios of omega-3 fatty acids to shape guidance for women in the earliest stages of their motherhood journey.

DHA Supplementation and Female Fertility

Few studies have explored if DHA supplementation can improve fertility outcomes. In the prospective "Time to Conceive" study of 900 women, those who reported taking an omega-3 supplement had 1.5 times (95% CI 1.12-2.04) the probability of conceiving compared to those not taking an omega-3 supplement, suggesting that omega-3 supplementation may improve fertility.[128] In a small RCT, 120 sub fertile women undergoing IVF were randomized to receive 1,000 mg of omega-3 fatty acids (including 120 mg of DHA) or a placebo for eight weeks.[129] Compared to those in the placebo group, women in the supplementation group had improved fertility outcomes such as the number of mature oocytes, fertilization rate (52% vs. 68%, *P*<0.05), and the number of grade 1 embryos (0.67 +/- 0.13 vs. 2.16 +/-0.28, *P*<0.001).[129]

Another small RCT was conducted among 34 women with polycystic ovary syndrome (PCOS)-related infertility undergoing ovulation induction treatment.[130] They were randomized to 1,800 mg of omega-3 (including 720 mg of DHA) or a placebo for a maximum of 2 menstrual cycles. Results showed a greater number of clinical pregnancies in the omega-3 supplement group compared to the placebo group (26.7% vs. 13.3%, *P*=0.1), especially among obese women (29.6% vs. 5.3%, *P*=0.04).[130] This is an emerging area, and more clinical trials are needed to determine if omega-3 supplementation – and DHA specifically – can improve pregnancy rates in both healthy and infertile women.

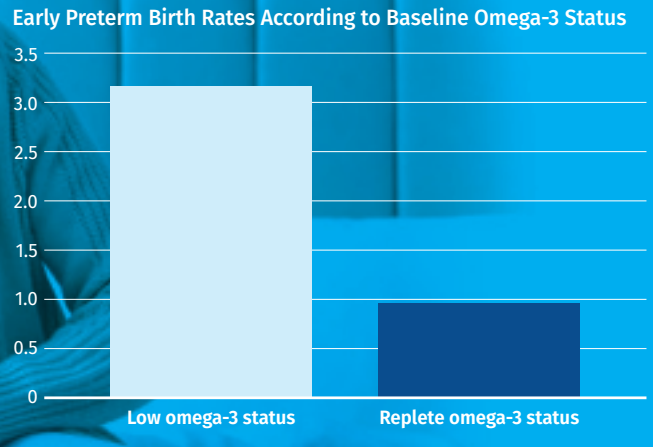


DHA and Pregnancy

The importance of omega-3 fatty acids for fetal brain development is undisputed.[117] During the last trimester of pregnancy, the placenta preferentially transfers DHA to the fetus. The fact that this particular omega-3 is prioritized over other fatty acids signals its importance in fetal development.[131] In the brain, various types of phosphoglycerides – critical for processes like signal transduction and memory formation – have DHA profiles.[115,132] In addition, DHA is a precursor for metabolites such as prostaglandins, leukotrienes, resolvins, and endocannabinoids; these substrates modulate the central and enteric nervous systems.[115] A recent systematic review reported that DHA intakes during pregnancy are positively correlated with desirable neurodevelopment outcomes in infants and children.[117]

DHA intake is also associated with other pregnancy outcomes. In a meta-analysis of 12 studies on omega-3 fatty acid blood levels in pregnant women, those with perinatal depression had low levels of DHA and total omega-3 PUFAS, and an increased ratio of omega-6 to omega-3 fatty acids compared to heathy controls.[133] Several population cohort studies have shown associations between fish intakes during pregnancy and reduced risk of preterm births, and at a population level, preterm birth rates decrease as omega-3 fatty acid levels increase.[134-138] Further, a convincing body of evidence demonstrates that women entering pregnancy with low DHA intakes and/or levels are at an increased risk of preterm delivery compared to those with adequate intakes and levels, suggesting that pre-conception DHA levels play an influential role in later pregnancy outcomes.[30,139,140] The link between a mother's baseline DHA status and preterm birth is illustrated in **Figure 10**.

Figure 10: **Baseline maternal omega-3 status influences the risk of premature delivery**[30]



Omega-3 DHA Supplementation and Pregnancy Outcomes

There have been several trials assessing the impact of omega-3 supplementation during pregnancy on maternal and infant outcomes; these were synthesized in a Cochrane systematic review.[120] High-quality evidence showed that the addition of omega-3 fatty acids during pregnancy reduced the risk of having an infant with LBW (15.6% versus 14%; RR 0.90, 95% CI 0.82-0.99; 15 trials, 8,449 participants).[120] However, the authors found a possible increased risk of having a large for gestational age (LGA) baby (RR 1.15, 95% CI 0.97-1.36; 6 RCTs, 3,722 participants; moderate-quality evidence). In addition, the review also showed a potential for the reduced risk of perinatal death (RR 0.75, 95% CI 0.54-1.03; 10 RCTs, 7,416 participants; moderate-quality evidence) and fewer neonatal intensive care admissions (RR 0.92, 95% CI 0.83-1.03; 9 RCTs, 6,920 participants; moderate-quality evidence) with omega-3 fatty acid supplementation during pregnancy. Very few differences were observed in long term neurodevelopment outcomes in children. The review also evaluated maternal outcomes: omega-3 fatty acid supplementation during pregnancy possibly reduced the incidence of pre-eclampsia, although the quality of evidence was low (RR 0.84, 95% CI 0.69-1.01; 20 trials, 8,306 participants).[120]

Omega-3 DHA for Preterm Birth Risk Reduction

The most noteworthy findings of the review were related to premature birth. Compared to women who did not take supplemental omega-3 fatty acids, those who did had longer gestations (mean difference [MD] 1.67 days, 95% CI 0.95-2.39; 41 trials, 12,517 participants; moderate-quality evidence) and a lower risk of preterm (<37 weeks gestation) (13.4% versus 11.9%; RR 0.89, 95% CI 0.81-0.97; 26 RCTs, 10,304 participants; high-quality evidence) and early preterm births (<34 weeks gestation) (4.6% versus 2.7%; RR 0.58, 95% CI: 0.44-0.77; 9 RCTs, 5,204 participants; high-quality evidence).[120] The results were largely driven by trials that used daily doses of 600-1,000 mg of omega-3 fatty acids, and study results were more compelling in trials that used DHA only or DHA-predominant fatty acid blends.

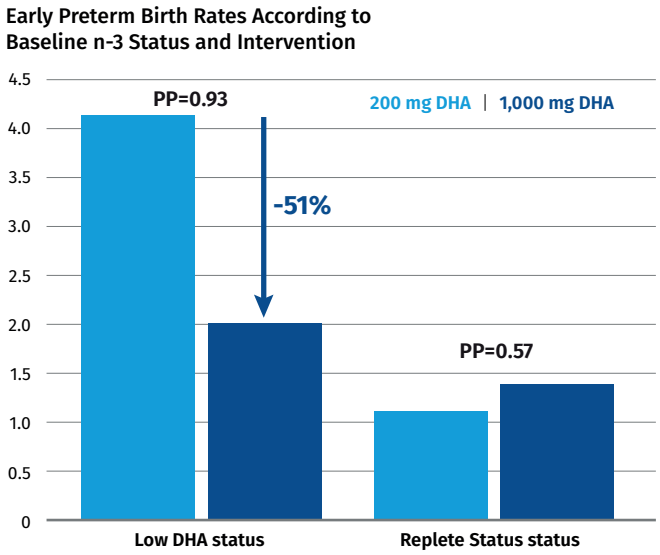
Three large RCTs exploring the impact of omega-3 fatty acid supplementation on preterm birth rates have been published since the Cochrane review.[30,140,141] The meta-analyses for preterm and early preterm birth were recently updated to include the newer trials and confirmed the findings from the Cochrane review.[119] Best et al., found with high-certainty evidence that omega-3 fatty acid supplementation compared to no supplementation or low-dose fatty acid supplementation reduced the risk of preterm births by 12% (RR 0.88, 95% CI 0.81-0.95; 36 trials, 23,726 participants) and early preterm births by 35% (RR 0.65, 95% CI 0.46-0.92; 12 trials, 16,782 participants).[119] They also recognized that women who started supplementing with omega-3 fatty acids or who had adequate dietary intakes of omega-3 fats early in pregnancy were at a reduced risk of preterm birth and should maintain those intakes throughout pregnancy. However, women with low omega-3 fatty acid intakes early in pregnancy benefit most from high dose omega-3 fatty acid supplementation, starting before 20 weeks of pregnancy and continuing until birth.[119]

Illustrating this finding, in the ADORE trial by Carlson et al., a total of 1,100 pregnant women in the U.S. were randomized to receive either a high dose (1,000 mg/day) or a low dose (200 mg/day) of algal omega-3 DHA. Preterm and early preterm birth rates were reduced in the high dose group compared to the low dose group (preterm birth: 10.5% vs. 13.1%, posterior probability [pp] 0.95; early preterm birth: 1.7% vs. 2.4%, pp 0.81).[30] The findings were even more compelling in the per protocol analysis: women who were compliant with the high dose regimen had a 43% reduction in preterm birth (11.0% vs. 6.3%, pp 1.00) and a 50% reduction in early preterm birth (2.4% vs. 1.2%, pp 0.93) compared to those in the low dose group.[142]

PP: posterior probability

The ADORE trial also evaluated baseline maternal DHA blood status and DHA intake via a validated food frequency questionnaire.[30] Although all women who adhered to taking the supplement benefited from the high dose, those who entered the study with low DHA intake benefited the most. As shown in **Figure 11**, women with low DHA status at enrollment who were randomized to the high dose of DHA (1,000 mg/day) had half the incidence of early preterm birth compared to those who had low DHA status at enrollment and who were randomized to the lower dose (200 mg/day) (2% vs. 4.1%, pp 0.93).[30] This suggests that supplementing with the amount of DHA typically found in prenatal supplements – 200 mg per day – is insufficient to reduce the risk of preterm birth, especially among women with low DHA intake early in pregnancy.

Figure 11: **Early preterm birth rates were influenced by baseline DHA status and the dose of DHA supplementation in the ADORE trial**[30]



Unfortunately, women are not routinely screened for blood DHA status in early pregnancy, and there is no consensus on the blood fractions that should be measured or the levels that should be used to determine low and replete status.[143] Implementing a universal screening strategy based on blood measures may be challenging, and even impossible in some populations. The validated food frequency questionnaire utilized in the ADORE trial was able to identify women who would benefit most from high dose DHA supplementation. This simple and inexpensive tool was successfully implemented as the standard of care for screening all pregnant women at a U.S. university medical center.[144]

Omega-3 DHA Supplementation Recommendations for Women of Childbearing Age and Pregnant Women

As the evidence grows that omega-3 DHA intakes before and during pregnancy can reduce the risk of preterm birth, expert bodies have begun issuing recommendations for omega-3 DHA supplementation during pregnancy (see **Table 3**). Given the findings that women with low baseline omega-3 PUFA intakes or status are at increased risk of preterm birth and early preterm birth, ensuring women have adequate omega-3 PUFA intakes before pregnancy may be the most effective strategy to reduce the rates of preterm birth.[30,139,140] When it is not possible to assess early pregnancy baseline omega-3 PUFA status, healthcare professionals may advise pregnant women to supplement with a moderate dose of DHA (450-600 mg per day), which is supported with expert guidelines, population level studies, and a clinical trial showing that 600 mg of DHA per day reduced the risk of early preterm birth in a largely omega-3 deficient pregnant population.[134,135,145,146]

For women who have been identified as having low DHA status or intake early in pregnancy, the most recent clinical trials indicate a higher dose of 1,000 mg DHA may be appropriate.[30,119] Other medical guidelines align with the focus that DHA status and the risk of preterm birth should be considered in advising on DHA supplementation. Pregnant women who take supplements have significantly higher DHA intakes and are 10 times more likely to have intakes that meet minimum recommended levels of 200 mg/day.[147]

Table 3: **Omega 3 DHA Supplementation Recommendations for Pregnant Women**

Organization	DHA Supplement Recommendations
Polish Society of Gynecologists & Obstetricians[148]	Supplement at least 200 mg DHA in all pregnant women Consider higher-dose DHA in women consuming small amounts of fish during pregnancy and in the preconception period Use 1,000 mg DHA daily in women at risk of premature birth
Australian Department of Health[111]	Supplementation with omega-3 LCPUFA (800 mg DHA and 100 mg EPA per day) may reduce the risk of preterm birth among women who are low in omega-3
International Society for the Study of Fatty Acids and Lipids[119]	Adequate intake of omega-3 LCPUFA in early pregnancy, consistent with existing nutritional guidelines, is associated with a lower risk in preterm and early preterm birth for women with singleton pregnancies. Women with adequate intake of omega-3 LCPUFA in early pregnancy should be encouraged to maintain their intakes. Women who are low in omega-3 fatty acids will benefit most from omega-3 LCPUFA supplementation to reduce their risk of early birth. In such cases, supplementation with a total of ~1,000 mg of EPA plus DHA is recommended. Supplementation should commence before 20 weeks gestation. Routine maternal screening for omega-3 depletion in early pregnancy is recommended to identify women who would benefit from specific supplementation. Assessment of omega-3 status in blood is ideal.

3.4. The Role of Vitamin D in Female Fertility and Pregnancy

Vitamin D is an essential nutrient produced in the skin after sun exposure. It is unique among vitamins since it functions as a hormone. The two main forms of dietary vitamin D are cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). Vitamin D3 is mainly found in animal foods such as fatty fish and egg yolks, while vitamin D2 is found vegetarian sources like mushrooms. Both forms are available in dietary supplements and fortified foods. After absorption, both vitamin D2 and D3 are converted to 25-hydroxyvitamin D (25[OH]D) in the liver. Another enzymatic hydroxylation reaction in the kidney transforms 25(OH)D to the biologically active form of vitamin D, calcitriol.[149]

Although the science is evolving, vitamin D appears to influence hormones that influence follicle development and suppression of ovarian maturation, both of which are important for fertility.[150,151] Vitamin D also seems to directly impact the success of embryo implantation in the uterus. Vitamin D receptors have been identified in human maternal uterine tissue, and calcitriol regulates transcription of a key gene associated with embryo implantation.[152] During pregnancy, vitamin D is best known for its roles in bone development and in aiding the absorption and retention of calcium and phosphorous, minerals important for healthy fetal development. Vitamin D is known to impact immune homeostasis, incidence of infection, proinflammatory cytokines, and vasoconstriction, all mechanisms thought to be involved in the development of both preeclampsia and prematurity.[32,153]

Vitamin D Deficiency

Since vitamin D is synthesized in the skin after sun exposure, modern trends of spending more time indoors and using sunblock have increased the prevalence of vitamin D deficiency.[154] People with darker skin tones synthesize less vitamin D from sun exposure compared to those with lighter skin tones.[154,155] Overt vitamin D deficiency results in osteomalacia in adults. This is uncommon in developed nations, but subclinical deficiencies are prevalent, especially in pregnant women.[154] Subclinical vitamin D deficiency is associated with an increased risk of autoimmune, cardiovascular, neurogenerative, and infectious diseases in adults.[156] Globally, an estimated 54% of pregnant women have vitamin D deficiency (25[OH]D <50 nmol/L) and 18% have severe vitamin D deficiency (25[OH]D <25 nmol/L). Vitamin D deficiency rates among pregnant women range from 46% in the Eastern Mediterranean to 87% in Southeast Asia. In the Americas and Europe, an estimated 64% and 57% of pregnant women have a vitamin D deficiency, respectively.[154]

Vitamin D and Female Fertility

In northern countries, there are seasonal peaks in pregnancy rates during summer and autumn. This coincides with seasons with more sunlight and when higher blood 25(OH)D levels are observed, leading to the hypothesis that vitamin D supports fertility.[157,158] According to a recent meta-analysis, among women undergoing ART, those with adequate vitamin D levels had more clinical pregnancies (odds ratio [OR] 1.46, 95% CI 1.05-2.02) and live births (OR 1.22, 95% CI 1.08-1.65) compared to those who had insufficient status.[157,159]

Lower levels of vitamin D during early pregnancy have also been associated with increased risk of early and recurrent spontaneous abortions. In an observational study, vitamin D deficiency during the first trimester was linked to a greater than two-fold risk of miscarriage.[160] Further, a meta-analysis evaluated data from 14 clinical studies and showed that women with recurrent spontaneous abortions had significantly lower vitamin D levels compared to controls (P<0.001) and pregnant women with vitamin D deficiency might be at a 4 times higher risk for recurrent spontaneous abortions (OR 4.02, P<0.001).[161]

In a similar meta-analysis of 10 studies and over 7,000 women, those with vitamin D deficiency (25(OH)D <50 nmol/L) had almost double the risk of spontaneous abortion when compared with women who were vitamin D replete (25(OH)D >75 nmol/L) (OR 1.94; 95% CI 1.25-3.02).[33] Even when women who were either vitamin D insufficient (25(OH)D = 50–75 nmol/L) or deficient (25(OH)D <50 nmol/L) were compared with women who were vitamin D replete (25(OH)D >75 nmol/L), an association to early miscarriage remained (OR 1.60; 95% CI 1.11-2.30).[33] Given the body of evidence, it appears that an adequate vitamin D status is important to optimize female fertility.

Vitamin D Supplementation and Female Fertility

Although studies exploring links between vitamin D supplementation in natural female fertility are lacking, emerging data suggest supplementation might improve success of IVF.[162] A meta-analysis of 12 studies including 2,352 infertile women found that clinical pregnancy rates (fetal heartbeat confirmed by ultrasound) were increased by 70% in women receiving vitamin D supplementation compared to those without (OR 1.70, 95% CI 1.24-2.34).[152] No significant differences were observed for implantation rates (the percentage of embryos that successfully implanted confirmed by ultrasound) or miscarriage rates. The level of improvement in pregnancy rate was influenced by the vitamin D status of the women, dosage of vitamin D, and duration of supplementation. The authors conclude that infertile women with vitamin D levels below 75 nmol/L and supplemented with 1,000-10,000 IU daily for 30-60 days could improve their chances of pregnancy.[152]

Vitamin D During Pregnancy

Studies have demonstrated that insufficient vitamin D status during pregnancy is associated with several adverse outcomes including gestational diabetes, pregnancy-induced hypertension, prematurity, and having an infant born SGA.[163] A prospective cohort study of almost 5,000 pregnant women in China revealed that, when compared to women with severe vitamin D deficiency (25[OH]D <25 nmol/L), women with blood 25(OH)D levels between 50-75 nmol/L had a ~25% reduced risk of developing gestational diabetes, and this increased to a 60% reduction in women with blood 25(OH)D levels >75 nmol/L.[164] These findings were confirmed in a meta-analysis of 20 observational studies and 28,982 pregnant women, where vitamin D insufficiency was associated with a 39% increased risk of developing gestational diabetes (pooled OR 1.39, 95% CI 1.20-1.60).[165]

Similar associations have been found between vitamin D status and pregnancy-induced hypertension. Women with preeclampsia had significantly lower vitamin D levels compared to healthy pregnant women in a nested case control study (median (IQR) = 43.3 [35.5, 55.2] versus 47.5 [37.6, 60.4] nmol/L, *P* =.014).[166] In a meta-analysis of 22 studies including 25,530 pregnant women, those with vitamin D insufficiency or deficiency had a 58% higher risk of preeclampsia compared to women with sufficient vitamin D levels (OR 1.58, 95% CI 1.39-1.79).[32]

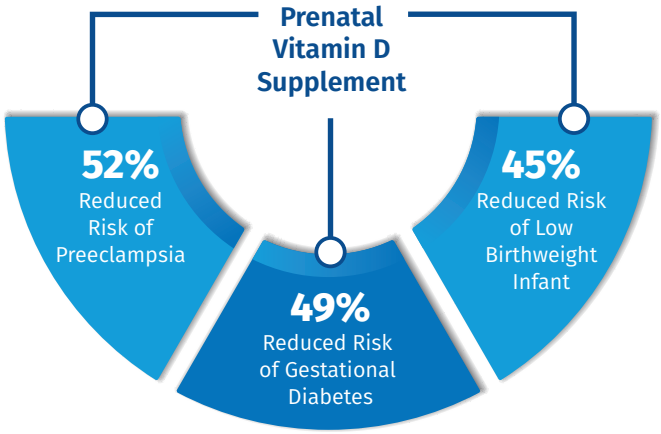
Women with vitamin D deficiency are also at an increased risk for preterm birth and having infants born SGA. A retrospective study at a large urban medical center in the U.S. found gestational length increased as vitamin D levels increased.[167] A similar finding was observed in a meta-analysis of 31 trials. A linear dose-response analysis showed that each 25 nmol/L increase in 25(OH)D was associated with a 6% reduction in the risk of preterm birth (RR 0.94; 95% CI 0.90–0.98).[168] In the same study, there was also a linear- dose response for vitamin D levels and having an infant born SGA. Each 25 nmol/L increase in 25(OH)D was associated with a 10% reduction in risk (RR 0.90; 95% CI 0.84-0.97).[168] In a meta-analysis of 13 cohort studies with a sample of over 28,000 individuals from seven countries, the pooled overall odds ratio for babies born SGA was 1.588 (95% CI 1.138-2.216; *P*<0.01) for women with vitamin D deficiency.[169] Longer-term effects of pregnancy vitamin D status have also been explored: deficiency during pregnancy has been associated with multiple negative sequelae including a higher risk of childhood asthma, language difficulties, and autism, but more studies are needed.[25]

Vitamin D Supplementation and Pregnancy Outcomes

A 2019 Cochrane review examined if vitamin D supplementation during pregnancy improved maternal and fetal outcomes.[170] The analysis included 22 trials involving 3,725 pregnant women. Compared to women taking a placebo or no intervention, women who took a vitamin D supplement had a 52% reduced risk of preeclampsia (RR 0.48, 95% CI 0.30-0.79; 4 trials, 499 women, moderate-certainty evidence), a 49% reduced risk of gestational diabetes (RR 0.51, 95% CI 0.27-0.97; 4 trials, 446 women, moderate-certainty evidence), and a 45% reduced risk of having a LBW infant (RR 0.55, 95% CI 0.35-0.87; 5 trials, 697 women, moderate-certainty evidence), as shown in **Figure 12**. Supplementation did not appear to significantly reduce preterm birth risk (RR 0.66, 95% CI 0.34-1.30; 7 trials, 1640 women, low-certainty evidence).[170] These findings are consistent with a more recent meta-analysis comparing high-dose vitamin D supplementation (>2,000 IU/day) with lower doses or a placebo during pregnancy that found no difference in preterm birth risk.[171]

Supplementation during pregnancy may also impact infant health. Another recent meta-analysis found an association between vitamin D supplementation and improved fetal linear growth, improved infant vitamin D status, and reduced fetal or neonatal mortality.[172] Additional studies of vitamin D supplementation during pregnancy, especially among women with vitamin D deficiency, are needed.

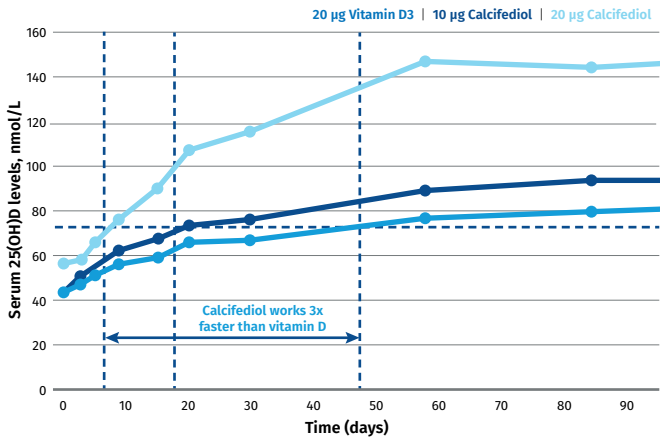
Figure 12: **Vitamin D supplementation during pregnancy improves maternal and infant outcomes**[170]



Calcifediol: An alternative to Vitamin D2 and Vitamin D3 supplementation

Currently, cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are the most widely used vitamin D supplements, but evidence is growing that calcifediol is a more bioavailable form.[173-177] In non-pregnant study participants, supplementation with calcifediol resulted in a more rapid increase in serum 25(OH)D compared to vitamin D3, as shown in **Figure 13**.[175] This may be partly related to a higher intestinal absorption rate of calcifediol along with it not requiring enzymatic conversion.[173,176] Although studies in pregnant women are lacking, calcifediol may be a more favorable option than vitamin D3 for two reasons: its ability to achieve optimal vitamin D status faster and with smaller doses.[176-178] Since compliance with supplement regimens involving large capsules during pregnancy are a known challenge, smaller doses may be especially beneficial.[142]

Figure 13: **Effect of supplementation of cholecalciferol (vitamin D3) compared to calcifediol on serum 25-hydroxyvitamin D status**[175]



Vitamin D Supplementation Recommendations for Women of Childbearing Age and Pregnant Women

Supplement recommendations during pregnancy are inconsistent, but in general, prophylactic supplementation is not recommended to avoid adverse pregnancy outcomes (see **Table 4**).[179] WHO recommends universal vitamin D supplementation as part of a MMS.[11] Universal screening for deficiency is also not typically recommended, but when identified, high dose supplementation is recommended.[179] Given the high prevalence of vitamin D deficiency during pregnancy, routine supplement and screening recommendations may need to be revisited.

Table 4: **Vitamin D Supplementation Recommendations for Pregnant Women**

Organization	DHA Supplement Recommendations
American College of Obstetricians and Gynecologists[179]	Pregnant women should supplement with the dose of vitamin D found in a standard prenatal vitamin until more evidence is available to support a specific dose. When vitamin D deficiency is identified during pregnancy, most experts agree that 1,000–2,000 IU per day of vitamin D is safe.
The International Federation of Gynecology and Obstetrics[180]	Women at high risk for deficiency* should supplement with at least 400 IU/day * Vegetarians, dark skinned individuals, those who live in environments with minimal sun exposure or who routinely wear sunblock
Australia Department of Health[111]	Routine testing for vitamin D status in pregnant women is not recommended without a specific indication. If testing is performed, vitamin D supplementation is recommended for women with 25(OH)D levels <50 nmol/L.
World Health Organization[11]	Supplement with a multiple micronutrient supplement including 200 IU Vitamin D.

3.5. The Role of Choline in Female Fertility and Pregnancy

Choline is an essential nutrient found predominantly in animal foods, with eggs and milk being especially good sources. Choline is necessary for lipid metabolism and cellular repair as well as liver, muscle, and brain function. It is required to make acetylcholine, an important neurotransmitter.[181] Like folate, choline is a methyl-donor nutrient, which means it plays a role in DNA methylation. Therefore, it can influence gene expression, a process central to conception and healthy fetal development.[35,181] During early development of the brain and nervous system, choline influences stem cell proliferation, altering brain and spinal cord structure and making it a key nutrient for preventing NTDs. It is also thought to be involved in the expression of genes that regulate learning, memory, and synaptic plasticity.[35,182,183] Choline is transferred across the placenta in large amounts during pregnancy, and choline concentrations in amniotic fluid and in umbilical cord and fetal plasma are significantly higher than in maternal blood or plasma, signaling an influential role for this nutrient in early development.[35]

Inadequate Choline Intakes

The recommended intake of choline increases during pregnancy, yet the vast majority of pregnant women fail to consume adequate choline through diet alone.[181] A National Health and Nutrition Examination Survey analysis revealed that only ~8% of pregnant women in the U.S. had choline intakes above the adequate intake level (450 mg).[184] The situation is similar in other regions including Europe and Australia. A comprehensive review of 23 dietary intake studies found that the average intake of choline among women of childbearing years ranged from 233-383 mg/day, falling below current recommendations.[185] Many prenatal vitamins do not contain choline, and when they do, levels are typically below the adequate intake level.[25] It is unclear why many vitamins do not contain choline, but it may be due to sensory and application issues with the nutrient.

Choline and Female Fertility

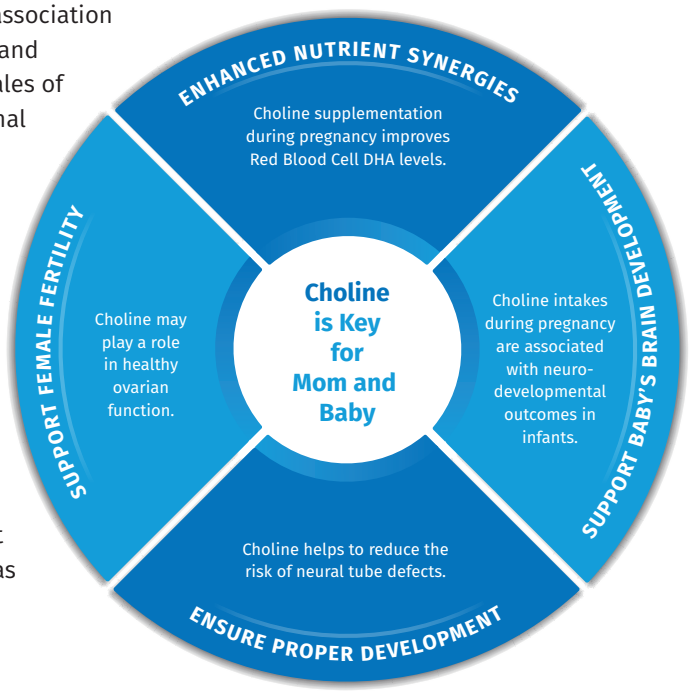
Very little is known about the relationship between choline intake or supplementation and female fertility outcomes. Given that choline plays a key role in reducing the risk of NTDs, which are a common cause of early fetal demise, it is likely that choline has an impact on fertility.[186,187] PCOS is a metabolic disorder that reduces female fertility. Plasma and follicular fluid choline levels are lower in women with PCOS compared to healthy women, suggesting choline may play a role in ovarian function.[187-189] Animal studies suggest that the addition of choline improves ovarian function, but human trials are needed.[187]

Choline and Pregnancy

Due to its role in the mitigating the risk of NTDs, optimizing choline intake prior to or in the earliest stages of pregnancy is vital.[35,190,191] A recent meta-analysis and systematic review studying the associations between prenatal and early postnatal choline intake, brain development, and neurocognitive function in children found that low maternal choline intakes were associated with a higher odds ratio for NTDs, up to 2.36-fold in some populations.[34] In a large prospective study that followed more than 180,000 pregnant women, serum levels of the nutrient were assessed in pregnancies affected by NTDs. Lower levels of total serum choline were associated with an elevated NTD risk, and conversely, a reduced risk was linked to higher levels of choline.[192]

Studies have also evaluated maternal choline status and infant cognitive outcomes. A prospective observational study found a positive association between maternal plasma choline levels at 16 weeks gestation and infant neurodevelopment scores (as assessed by the Bayley Scales of Infant Development-III) at 18 months of age.[193] In an observational study that assessed the longer-term impacts of early choline exposure, maternal intake of choline was linked to cognitive abilities in children 7 years later. Seven year old children whose mothers had consumed approximately twice the daily recommended adequate intake (AI) of choline (930 mg/day vs. pregnancy AI of 450 mg/day) during the third trimester of pregnancy performed better on a task that required sustained attention compared to children whose mothers consumed the AI of choline.[194] These findings are congruent with another study that found positive associations between early pregnancy choline intake and visual memory at 7 years of age. Higher second trimester choline intake - and intake that was near the AI for pregnancy (406 mg/day vs. 253 mg/day) - was associated with modestly better visual memory at age 7 years, compared to intake that was approximately 50% of the pregnancy AI for choline.[195] Collectively, these findings illustrate the potential neuroprotective effects of optimizing choline intake during pregnancy, but more studies are needed.

Figure 14: **Overview of the potential benefits of choline for mother and baby**[188,192,193,196]



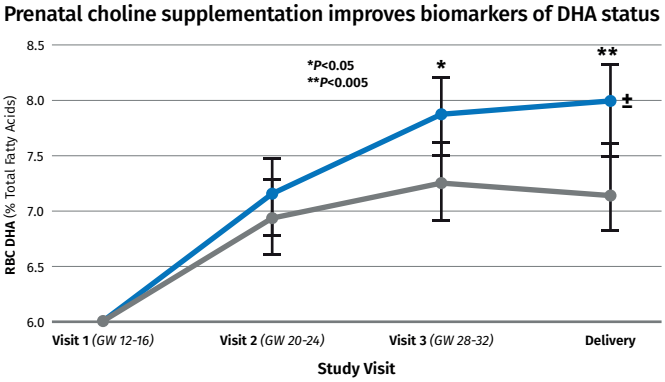
Choline Supplementation and Pregnancy Outcomes

Only a few small RCTs have explored the impact of choline supplementation on pregnancy outcomes in healthy women.[34] In Caudill et al., 24 pregnant women were randomized to either 100 mg or 550 mg of choline supplementation in the third trimester. The infants of mothers who received the higher dose of choline had faster measures of reaction time – a measure of neurodevelopment – compared to those who received the lower dose.[197] In another trial, 100 pregnant women were randomized to 900 mg of choline or a placebo for the last two trimesters of pregnancy. More infants in the choline group had the desired response to an auditory response test compared to those in the placebo group, but no differences were observed at other time points or for other neurodevelopmental outcomes.[198] Cheatham et al. randomized 140 pregnant women to 750 mg choline or a placebo from 18 weeks of pregnancy through 90 days postpartum. No differences in measures of neurodevelopment were observed in the infants up to 12 months of age.[199] Still, a systematic review of human data on the inter-relationships between choline, neurological development and brain function during the first 1,000 days of life was recently conducted. The authors concluded that maternal or child supplementation with choline during the critical first 1,000 days could support normal brain development, protect against in-utero neural insults, and improve cognitive and neural functioning.[34]

Choline and DHA: Synergies Between Two Key Brain Nutrients

As a methyl donor, choline supports the activity of the phosphatidylethanolamine N-methyltransferase (PEMT) pathway, which generates molecules enriched in DHA; these are exported from the liver and then made available to extrahepatic tissues. Scientists recently investigated whether prenatal choline supplementation would influence biomarkers of DHA status in pregnant women consuming DHA supplements. They found that, indeed, choline supplementation did yield higher RBC cell DHA levels at 28 to 32 weeks of pregnancy ($P<0.05$) and at the time of delivery ($P<0.005$), as seen in **Figure 15**. The identification of this nutrient-nutrient interaction suggests that the efficacy of DHA may be influenced by whether choline intake is sufficient. This key learning should be applied to future studies on these two nutrients known to be influential in both maternal and infant outcomes.[196]

Figure 15: **The effect of prenatal choline supplementation on biomarkers of DHA status among pregnant women who were also consuming supplemental DHA, compared to controls**[196]



Choline Supplement Recommendations for Pregnant Women

There is currently a lack of expert recommendations for choline supplementation during pregnancy. The International Federation of Gynecology and Obstetrics (FIGO) states there are potential benefits of supplementation and acknowledges that most prenatal vitamins have inadequate choline levels. In one assessment of prenatal vitamins in the U.S., only 40% contained choline, and the median level was 25 mg, far below the recommended intake of 450 mg.[25] Formulating vitamins with choline presents challenges, including the large size of the molecule and its unfavorable sensory profile.

Table 5: **Choline Supplementation Recommendations for Pregnant Women**

Organization	Choline Supplement Recommendations
The International Federation of Gynecology and Obstetrics[180]	Multivitamin supplements containing choline (approximately 450 mg/day) may be helpful to maintain adequate choline status and protect against NTDs, though many available formulations do not contain choline

GW: gestational week

3.6. The Role of Carotenoids in Female Fertility and Pregnancy

Carotenoids Overview

Carotenoids are naturally occurring pigments found in plants, algae, and certain types of bacteria. The brightly colored molecules are responsible for the red, orange, and bright yellow hues of carotenoid-rich plants, fruits and vegetables such as sweet potatoes, watermelon, bell peppers, tomatoes, carrots, mangoes, and oranges. These fat-soluble compounds are thought to be – at least in part – responsible for the health benefits of these foods.[200] Carotenoids function as antioxidants in the human body, and some are also important dietary sources of vitamin A. There are more than 600 types of carotenoids; some of the most common are: α-carotene, β-carotene, lutein, zeaxanthin, and lycopene.[201]

Carotenoids are classified into two main groups: xanthophylls and carotenes. The xanthophyll class of carotenoids contain oxygen, often have a yellow pigment, and are often associated with eye health. Lutein and zeaxanthin are two specific xanthophyll carotenoids. The carotene carotenoids do not contain oxygen and are associated with red and orange pigments. Well-known carotenes are β-carotene and lycopene.[201,202]

The antioxidant properties of carotenoids have been widely studied in recent years, including for their potential to positively impact fertility. A summary of available evidence is below.

Carotenoid Intakes

Few studies have investigated carotenoid intake during pregnancy. Overall, intakes vary widely depending on the population studied and seasonal and geographical variation.[203] Plasma levels of carotenoids in pregnant women are a direct function of their intake of fruits and vegetables, a variable influenced by seasonal availability of these foods, overall access to fruits and vegetables, dietary habits, and potential changes in maternal diet during pregnancy.[204,205] Dietary supplements can also be a significant source of carotenoids. In the Norwegian Mother and Child Cohort Study, plasma carotenoids were higher in women who took supplements compared to those who did not.[205]

Currently, Dietary Reference Intakes (DRIs) for carotenoids overall do not exist, although blood concentrations <1,000 nmol/L have been associated with increased risks of developing chronic diseases, such as type 2 diabetes, cardiovascular disease, stroke, and certain types of cancer.[206] An analysis based on the National Health and Nutrition Examination Survey (NHANES) evaluated links between intakes of carotenoids and hypertension in U.S. adults; median (interquartile range [IQR]) total carotenoid intake ranged from 79.73 (112.79) µ/kg/day to 94.35 (129.79) µ/kg/day.[207] Based on the inverse relationship between carotenoid intake and hypertension, the authors recommended intakes of at least 100 µg/kg/day.[207] Some guidance is available for intake of individual carotenoids – like provitamin A carotenoids – though not for the entire group.[208] For certain populations such as smokers and asbestos workers, higher blood concentrations of carotenoids are associated with harmful effects.[206]

Carotenoids and Fertility

While multifactorial in nature, infertility is thought to be partly related to oxidative stress and low antioxidant status. Antioxidant levels have been shown to be associated with reproductive hormone concentrations in healthy women,[209] and studies have demonstrated a lower total antioxidant status in women with PCOS – a risk factor for infertility – and in the peritoneal fluid of women with infertility of unknown origin.[210,211]

To investigate this further, in a secondary data analysis of a RCT in couples being treated for unexplained infertility, researchers evaluated whether increased antioxidant intake in women was associated with a shorter time to pregnancy (TTP).[212] The relationship between various antioxidants and fertility varied. However, in multivariable models, intake of β-carotene from dietary supplements was associated with shorter TTP in women with a body mass index ≥25 kg/m(2) (HR 1.29, 95%CI 1.09-1.53) and in women <35 years of age (HR 1.19, 95% CI 1.01-1.41). β-carotene intake from dietary supplements seemed to be more relevant than intake from food, though a mechanism for this could not be explained by the study's authors.[212]

In a prospective cohort study in the U.S., the relationship between preconception levels of a number of antioxidants and TTP was assessed in 1,228 women with 1 to 2 prior pregnancy losses.[213] Serum levels of zeaxanthin, cryptoxanthin, lycopene, α-carotene, β-carotene, α-tocopherol and γ-tocopherol were measured in participants attempting pregnancy without the use of fertility treatments. The authors found that increased preconception serum carotenoid concentrations were linked to improved fecundability (OR 1.17, 95% CI 1.0-1.36) and shorter TTP (OR 1.21, 95% CI 1.02-1.44). Conversely, γ-tocopherol levels at or above the U.S. average were associated with a longer TTP.[213] While preliminary in nature, these findings suggest the potential for carotenoids to influence fecundability, a prospect that deserves more study.

The Impact of Carotenoids in Pregnancy Outcomes

Pre-eclampsia (PEC) is a major pregnancy complication with manifestations that include hypertension, proteinuria, and edema. PEC significantly increases the risk of negative pregnancy outcomes such as fetal growth restriction, premature delivery, and stillbirth. An imbalance between antioxidants and pro-oxidants is thought to contribute to PEC development.[214] A study investigated the association between maternal dietary carotenoid intake and pre-eclampsia in 880 pregnant women in China.[215] Food-frequency questionnaires were used to assess dietary intake of carotenoids. After adjusting for confounders, the researchers found that the intakes of total carotenoids, β-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin were negatively associated with the odds of developing PEC. When compared to the lowest quartile intake, the adjusted odds ratio (95% CI) for the highest quartile intake was as follows: total carotenoids (OR 0.29, 95% CI 0.16–0.54, $P < 0.001$); β-carotene (OR 0.31, 95% CI 0.16–0.5, $P<0.001$); β-cryptoxanthin (OR 0.50, 95% CI 0.27–0.90, $P=0.007$); lycopene (OR 0.55, 95% CI 0.30–0.99, $P=0.04$); and lutein-zeaxanthin (OR 0.32, 95% CI 0.17–0.61, $P = 0.001$).[215] These findings are in alignment with those of other studies showing positive impacts of increased maternal carotenoid concentrations on PEC.[216,217]

A Focus on Lutein and Zeaxanthin

Lutein and zeaxanthin are carotenoids that are well-recognized for their roles in supporting eye health.[36] Recently, researchers investigated carotenoid levels in the placenta and umbilical cord of infants, and found higher levels of lutein and zeaxanthin that any other carotenoid (49% and 37%, respectively). In addition, the rate of transfer of lutein and zeaxanthin from maternal to fetal cord blood was the highest of all carotenoids.[218] These carotenoids have been studied in premature infants – a population at high-risk for eye disease – for whether their addition to human milk could support retina maturation.[219] In an RCT of 203 infants <33 weeks gestation, lutein and zeaxanthin supplementation resulted in greater rod photoreceptor sensitivity (P<.05), one marker of vision and overall retinal function. Additionally, supplemented infants had lower plasma C-reactive protein (P<.001), a measure of inflammation.[219]

Studies have examined whether early exposure to lutein and zeaxanthin leads to long-term benefits for visual health. Maternal concentrations of lutein and zeaxanthin at delivery were assessed for a relationship to visual acuity (VA) in 3 year olds.[220] The highest tertile of maternal zeaxanthin concentration was associated with 38% lower likelihood of poor VA in children (95% CI 0.42-0.93, p-Trends = 0.02). Higher maternal lutein concentrations were associated with a lower likelihood of poor VA in children (middle tertile: RR 0.60, 95% CI 0.40-0.88; highest tertile: RR 0.78, 95% CI 0.51-1.19) (p-Quadratic = 0.02).[220] These results are promising, but further studies with broader measures of vision and eye function are needed.

While several studies have established a role for lutein and zeaxanthin in eye development, evidence is accumulating for an important role for lutein in brain development.[221,222] This is unsurprising since the brain and eye share the same embryological origin in the neural tube. The fact that this carotenoid accumulates in areas of high metabolic demand and with increased oxidative stress suggests it may play a crucial role as an antioxidant during the development and maturation of these organ systems.[222] In a prospective cohort study, researchers evaluated whether lutein and zeaxanthin intake during pregnancy correlates to child cognitive development and measures of executive function.[37] Better scores on verbal intelligence and behavior regulation in children were linked to higher maternal intake of lutein and zeaxanthin during pregnancy, suggesting exposure to these carotenoids during early brain and cognitive development may indeed be important.[37]

Recommended Intakes of Carotenoids for Pregnant Women

While there are no DRIs for carotenoids as they are not considered essential nutrients, the importance of these substances to maternal and infant health can be inferred based upon other recommendations, such as the focus on fruit and vegetable intake across the lifespan and especially during pregnancy, the higher levels of carotenoids found in breastmilk compared to infant formula,[223] and the evidence for eye health benefits in adults who take lutein daily.[36,204,224]

3.7. Additional Emerging Nutrients for Fertility Support

As the relationship between nutrient intake and fertility continues to be studied, certain nutrients have recently emerged as having a potential positive impact on fertility. A brief overview of some of these nutrients and available data are discussed below.

Co-enzyme Q10 andFertility

Co-enzyme Q10 (CoQ10) is an antioxidant naturally produced by the body. It is essential for the production of energy and protects cells against oxidative damage. The highest levels are found in the heart, liver, kidneys and pancreas.[225,226] Studies have suggested that CoQ10 may have a positive effect on female fertility. Some research has shown that supplementation with CoQ10 may improve ovarian function and egg quality, as well as increase the chances of pregnancy in women undergoing IVF.[227-229] Additionally, studies have also explored the impact of CoQ10 on male fertility, and have found CoQ10 supplementation may improve sperm quality and motility, as well as reduce oxidative stress in the reproductive system.[230,231]

A systematic review and meta-analysis assessed the available evidence for the impact of CoQ10 on clinical pregnancy, live birth, and miscarriage rates compared with placebo or no treatment in women undergoing ART.[229] Five RCTs with a total of 449 women were included in the review. Oral supplementation with CoQ10 increased clinical pregnancy rates when compared with placebo or no treatment (28.8% vs. 14.1%, respectively; OR 2.44, 95% CI 1.30-4.59, *P*=0.006). When women with poor ovarian response and PCOS were analyzed separately, the effect remained significant. No differences in live birth rates or miscarriage rates were observed between groups.[229] Further studies are needed to confirm these findings and to determine the optimal dosage and duration of supplementation.

Cobalamin and Fertility

Cobalamin, or vitamin B12, is an essential nutrient required for many physiological processes, including DNA synthesis, RBC formation, and neurological function. Studies have also suggested that cobalamin plays an important role in fertility.[232] It is necessary for the proper functioning of the female reproductive system, and is involved in the development and maturation of ovarian follicles. Low levels of cobalamin have been linked to irregular menstrual cycles, ovulatory dysfunction, and early pregnancy loss.[25,233]

Cobalamin supplementation has been shown to improve fertility outcomes in both men and women. In women, supplementation with cobalamin and folic acid have been shown to increase the likelihood of ovulation and pregnancy in women undergoing fertility treatments.[234] In men, cobalamin supplementation has been associated with improved sperm parameters.[235] Whether this translates to improved pregnancy outcomes is unknown.

Overall, the available data suggest that cobalamin plays in important role in fertility, and that maintaining adequate levels of this essential nutrient may improve fertility outcomes. However, more research is needed to fully understand the mechanisms underlying the relationship between cobalamin and fertility, as well as to determine the optimal dosages and duration of supplementation needed to positively impact fertility outcomes.

Inositol and Fertility

Inositol is a sugar found in various fruits, beans, and nuts. It influences physiological processes such as insulin signaling and cellular membrane formation. In recent years, inositol has been studied for its potential effects on fertility in both men and women.

In women, inositol has been found to help regulate menstrual cycles and improve insulin sensitivity, both of which can increase the changes of ovulation and conception.[236] Specifically, two forms of inositol, myo-inositol and D-chiro-inositol, have shown benefits for women with PCOS-related infertility.[237] Studies have found that supplementation with both forms of inositol can improve menstrual regularity, increase the number of mature follicles, and improve pregnancy rates in this population.[238,239]

In men, inositol may assist in fertility by improving sperm quality.[240] Research is pointing to the benefits of supplementing with myo-inositol, alongside other antioxidants like selenium, for improved sperm concentration and motility in men with asthenozoospermia (low sperm motility).[241-243]

More research is needed to fully understand the links between inositol and fertility, but preliminary studies do suggest a beneficial effect for both men and women.

4 | Summary and Conclusions

The maternal journey – from the early stages of pregnancy up to the day of delivery – comprises immense and meaningful life changes for a woman. The changes that unfold during this time can drastically impact physical health. Nutrition plays such an important and influential role in supporting a woman through these changes, and provides much-needed nourishment for the demanding journey of motherhood. Further, the nutrition provided to the infant during their vulnerable early days will have ongoing impacts on their growth and development.

Advances in nutrition science are illuminating how diet and nutrient intakes can have significant and lasting positive impacts on both maternal and infant outcomes, and are thus guiding expert recommendations. While all nutrients are important during the sensitive stages of conception, pregnancy, and fetal development, certain nutrients are known to play a substantial role. Iron, folate, DHA, vitamin D, choline, and carotenoids are critical for the long-term health of both mother and baby. These nutrients have been shown to have significant impacts on the incidence of maternal anemia, the risk of preterm delivery, pregnancy and fertility-related outcomes, brain health and development, cognitive outcomes, and visual and eye health. Health policies and nutritional guidance for dietary intake and supplementation should ensure adequate access and delivery of these vital nutrients throughout the preconception and pregnancy stages.

5 | DSM Supports Maternal Nutrition

At DSM, we believe in the value of quality, sustainable, maternal nutrition to promote a healthy start in life – without impacting the planet.

With our consumer insights and scientific expertise, DSM's purpose-led solutions help you to nourish healthier and happier mothers and babies with key ingredients, such as *life'sDHA*® algal omega-3, while achieving more efficient speed-to-market. At DSM, we know life is healthier when it's supported from the beginning. That's why we're committed to delivering high-quality, insight-driven, innovative nutritional solutions at every stage of your product's development. This takes more than ingredients. It takes a partner. Partner with DSM for access to our broad portfolio of science-backed products, customized solutions, and expert services aimed at reliably supporting your entire product life cycle, from concept to consumer.

DSM provides:

- **High quality standards**
- **Focus on innovation and sustainability**
- **Expert services for application and formulation**
- **Strong on advocacy**

6 | Appendix

Table A1: **Recommended Daily Nutrient Intakes during Pregnancy by Authoritative Bodies**

	US National Academies RDA for Pregnancy[206]*	EFSA Dietary Reference Values for Nutrients[244]**
Calcium	1,300 mg (ages 14-18) 1,000 mg (ages 19-50)	860 mg (ages 18-24) 750 mg (ages 3-25)
Iron	27 mg	16 mg
Magnesium	400 mg (ages 14-18) 350-360 (ages 19-50)	300 mg
Phosphorus	1,250 mg (ages 14-18) 700 mg (ages 19-50)	550 mg
Potassium	2,600 mg (ages 14-18) 2,900 mg (ages 19-50)	3,500 mg
Sodium	2,300 mg	2,300 mg
Zinc	12 mg (ages 14-18) 11 mg (ages 19-50)	9.1-14.3 mg (baseline requirements for non-pregnant women, +1.6 mg)
Iodine	220 µg	200 µg
Choline	450 mg	480 mg
Vitamin A	750 µg RAE (ages 14-18) 770 µg RAE (ages 19-50)	700 mg
Vitamin E	15 mg	11 mg
Vitamin D	600 IU	600 IU
Vitamin C	80 mg (ages 14-18) 85 mg (ages 19-50)	105 mg
Thiamin	1.4 mg	1.4 mg
Riboflavin	1.4 mg	1.9 mg
Niacin	18 mg	PRI + 1.6 mg/day
Vitamin B6	1.9 mg	1.8 mg
Vitamin B12	2.6 µg	4.5 µg
Folic acid	600 µg DFE	500 µg DFE
Vitamin K	75 µg (ages 14-18) 90 µg (ages 19-50)	75 µg (ages 14-18) 90 µg (ages 19-50)
Omega-3 fatty acids	Two servings of fish per week (8-12 oz) to get desired amount of omega-3†	350-450 mg from EPA + DHA (250 mg for baseline adult requirements, +100-200 mg for pregnancy)

***** These guidelines have been adopted by the American College of Obstetricians and Gynecologists (ACOG); ****** Average Requirement or Adequate Intake;
US: United States; **RDA**: Recommended Dietary Allowances; **EFSA**: European Food Safety Authority; **RAE**: Retinol Activity Equivalents; **PRI**: Population Reference Intake;
DFE: Dietary Folate Equivalent; **†** From low mercury-containing fish and seafood.

Table A2: **Recommendations for Supplementation of Select Nutrients During Pregnancy**

Iron Supplementation Recommendations for Pregnant Women

Organization	Iron Supplement Recommendations
American College of Obstetricians and Gynecologists[65]	Screen all pregnant women for IDA and provide an iron supplement in addition to a prenatal vitamin to those with IDA.
United States Centers for Disease Control[66]	Supplement all pregnant women with low dose iron (30 mg/day) and screen for IDA. Women with IDA should supplement with 60-120 mg/day of iron.
European Food Safety Authority[68]	Supplement if at risk of IDA.
Australia Department of Health[111]	Advise iron supplementation to pregnant women based on their hemoglobin concentration at 28 weeks. Advise pregnant women taking an iron supplement that weekly supplementation (80-300 mg elemental iron) is as effective as daily supplementation (30-60 mg elemental iron) in preventing (but not treating) iron-deficiency anemia, with fewer adverse effects.
World Health Organization[11]	Supplement with a multiple micronutrient supplement including 30 mg of iron.

Folic Acid Supplementation Recommendations for Women of Childbearing Age and Pregnant Women

Organization	Folic Acid Supplement Recommendations
American College of Obstetricians and Gynecologists[110]	All women of childbearing age should supplement with 400 µg folic acid per day. Women with increased risk of NTDs should supplement with 4,000 µg/day.
United States Preventative Services Task Force[104]	Women who are planning or capable of pregnancy should take a daily supplement containing 400-800 µg folic acid.
Australia Department of Health[111]	Advise dietary supplementation of 400 µg per day folic acid, ideally from 1 month before conception and throughout the first 3 months of pregnancy to reduce the risk of NTDs.
World Health Organization[11]	Supplement with a multiple micronutrient supplement including 400 µg folic acid.

Omega 3 DHA Supplementation Recommendations for Pregnant Women

Organization	DHA Supplement Recommendations
Polish Society of Gynecologists & Obstetricians1[48]	Supplement at least 200 mg DHA in all pregnant women. Consider higher-dose DHA in women consuming small amounts of fish during pregnancy and in the preconception period. Use 1,000 mg DHA daily in women at risk of premature birth.
Australian Department of Health[111]	Supplementation with omega-3 LCPUFA (800 mg DHA and 100 mg EPA per day) may reduce the risk of preterm birth among women who are low in omega-3

Omega 3 DHA Supplementation Recommendations for Pregnant Women *continued*

International Society for the Study of Fatty Acids and Lipids[119]	Adequate intake of omega-3 LCPUFA in early pregnancy, consistent with existing nutritional guidelines, is associated with a lower risk in preterm and early preterm births for women with singleton pregnancies. Women with adequate intake of omega-3 LCPUFA in early pregnancy should be encouraged to maintain their intakes. Women who are low in omega-3 fatty acids will benefit most from omega-3 LCPUFA supplementation to reduce their risk of early birth. In such cases, supplementation with a total of ~ 1,000 mg of EPA plus DHA is recommended. Supplementation should commence before 20 weeks gestation. Routine maternal screening for omega-3 depletion in early pregnancy is recommended to identify women who would benefit from specific supplementation. Assessment of omega-3 status in blood is ideal.

Vitamin D Supplementation Recommendations for Pregnant Women

Organization	Vitamin D Supplement Recommendations
American College of Obstetricians and Gynecologists[179]	Pregnant women should supplement with the dose of vitamin D found in a standard prenatal vitamin until more evidence is available to support a specific dose. When vitamin D deficiency is identified during pregnancy, most experts agree that 1,000–2,000 IU per day of vitamin D is safe.
The International Federation of Gynecology and Obstetrics[180]	Women at high risk for deficiency* should supplement with at least 400 IU/day. **vegetarians, dark skinned individuals, those who live in environments with minimal sun exposure or who routinely wear sunblock*
Australia Department of Health[111]	Routine testing for vitamin D status in pregnant women is not recommended without a specific indication. If testing is performed, vitamin D supplementation is recommended for women with 25(OH)D levels <50 nmol/L.
World Health Organization[11]	Supplement with a multiple micronutrient supplement including 200 IU Vitamin D.

Choline Supplementation Recommendations for Pregnant Women

Organization	Choline Supplement Recommendations
The International Federation of Gynecology and Obstetrics[180]	Multivitamin supplements containing choline (approximately 450 mg/day) may be helpful to maintain adequate choline status and protect against NTDs, though many available formulations do not contain choline.

7 | References

1. Beluska-Turkan K, Korczak R, Hartell B, et al. Nutritional Gaps and Supplementation in the First 1,000 Days. *Nutrients*. 2019;11(12).

2. Alvarez P. What does the global decline of the fertility rate look like? . World Economic Forum. https://www.weforum.org/agenda/2022/06/global-decline-of-fertility-rates-visualised/. Published 2022. Accessed March 30, 2023.

3. World Health Organization. Infertility. https://www.who.int/health-topics/infertility#tab=tab_1. Published 2023. Accessed April 17, 2023.

4. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health*. 2019;7(1):e37-e46.

5. Cao G, Liu J, Liu M. Global, Regional, and National Incidence and Mortality of Neonatal Preterm Birth, 1990-2019. *JAMA Pediatrics*. 2022;176(8):787-796.

6. March of Dimes. Preterm Birth. https://www.marchofdimes.org/peristats/data?reg=99&top=3&stop=63&lev=1&slev=1&obj=1&sreg=99&creg. Updated January 2022. Accessed March 30, 2023.

7. Centers for Disease Control and Prevention. Severe Maternal Morbidity in the United States. Reproductive Health Web site. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/severematernalmorbidity.html. Updated February 2, 2021. Accessed March 30, 2023.

8. Osterman MJK, Hamilton BE, Martin JA, Driscoll AK, Valenzuela CP. Births: Final Data for 2021. *Natl Vital Stat Rep*. 2023;72(1):1-53.

9. Kominiarek MA, Rajan P. Nutrition Recommendations in Pregnancy and Lactation. *Med Clin North Am*. 2016;100(6):1199-1215.

10. Otten JJ, Pitzi Hellwig J, Meyers LD. Dietary reference intakes. *The essential guide to nutrient requirements*. Washington, DC: National Academies Press; 2006.

11. World Health Organization. WHO antenatal care recommendations for a postive pregnancy experience. *Nutritional interventions update: Multiple micronutrient supplements during pregnancy*. Geneva: World Health Organization 2020. Licence: CC BY-NC-SA 3.0 IGO.

12. Smith ER, Shankar AH, Wu LS, et al. Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries. *Lancet Glob Health*. 2017;5(11):e1090-e1100.

13. Haider BA, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database Syst Rev*. 2017;4(4):Cd004905.

14. Keats EC, Haider BA, Tam E, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database Syst Rev*. 2019;3(3):Cd004905.

15. Black RE, Dewey KG. Benefits of supplementation with multiple micronutrients in pregnancy. *Ann N Y Acad Sci*. 2019;1444(1):3-5.

16. Bourassa MW, Osendarp SJM, Adu-Afarwuah S, et al. Review of the evidence regarding the use of antenatal multiple micronutrient supplementation in low- and middle-income countries. *Ann N Y Acad Sci*. 2019;1444(1):6-21.

17. Schulze KJ, Mehra S, Shaikh S, et al. Antenatal Multiple Micronutrient Supplementation Compared to Iron-Folic Acid Affects Micronutrient Status but Does Not Eliminate Deficiencies in a Randomized Controlled Trial Among Pregnant Women of Rural Bangladesh. *J Nutr*. 2019;149(7):1260-1270.

18. Kashi B, C MG, Kurzawa ZA, Verney AMJ, Busch-Hallen JF, De-Regil LM. Multiple Micronutrient Supplements Are More Cost-effective Than Iron and Folic Acid: Modeling Results from 3 High-Burden Asian Countries. *J Nutr*. 2019;149(7):1222-1229.

19. Gaskins AJ, Chavarro JE. Diet and fertility: a review. *Am J Obstet Gynecol*. 2018;218(4):379-389.

20. The Lancet Global Health. Infertility-why the silence? *Lancet Glob Health*. 2022;10(6):e773.

21. Zegers-Hochschild F, Adamson GD, Dyer S, et al. The International Glossary on Infertility and Fertility Care, 2017. *Hum Reprod*. 2017;32(9):1786-1801.

22. Griesinger G, Dafopoulos K, Schultze-Mosgau A, Felberbaum R, Diedrich K. What is the most relevant standard of success in assisted reproduction?: Is BESST (birth emphasizing a successful singleton at term) truly the best? *Human Reproduction*. 2004;19(6):1239-1241.

23. Panth N, Gavarkovs A, Tamez M, Mattei J. The Influence of Diet on Fertility and the Implications for Public Health Nutrition in the United States. *Front Public Health*. 2018;6:211.

24. Montagnoli C, Santoro CB, Buzzi T, Bortolus R. Maternal periconceptional nutrition matters. A scoping review of the current literature. *J Matern Fetal Neonatal Med*. 2021:1-18.

25. Adams JB, Kirby JK, Sorensen JC, Pollard EL, Audhya T. Evidence based recommendations for an optimal prenatal supplement for women in the US: vitamins and related nutrients. *Matern Health Neonatol Perinatol*. 2022;8(1):4.

26. Georgieff MK. The role of iron in neurodevelopment: fetal iron deficiency and the developing hippocampus. *Biochem Soc Trans*. 2008;36(Pt 6):1267-1271.

27. Means RT. Iron Deficiency and Iron Deficiency Anemia: Implications and Impact in Pregnancy, Fetal Development, and Early Childhood Parameters. *Nutrients*. 2020;12(2).

28. Ars CL, Nijs IM, Marroun HE, et al. Prenatal folate, homocysteine and vitamin B(12) levels and child brain volumes, cognitive development and psychological functioning: the Generation R Study. *Br J Nutr*. 2019;122(s1):S1-s9.

29. Black MM. Effects of vitamin B12 and folate deficiency on brain development in children. *Food Nutr Bull*. 2008;29(2 Suppl):S126-131.

30. Carlson SE, Gajewski BJ, Valentine CJ, et al. Higher dose docosahexaenoic acid supplementation during pregnancy and early preterm birth: A randomised, double-blind, adaptive-design superiority trial. *EClinicalMedicine*. 2021.

31. Brenna JT, Carlson SE. Docosahexaenoic acid and human brain development: evidence that a dietary supply is needed for optimal development. *J Hum Evol*. 2014;77:99-106.

32. Hu KL, Zhang CX, Chen P, Zhang D, Hunt S. Vitamin D Levels in Early and Middle Pregnancy and Preeclampsia, a Systematic Review and Meta-Analysis. *Nutrients*. 2022;14(5).

33. Tamblyn JA, Pilarski NSP, Markland AD, et al. Vitamin D and miscarriage: a systematic review and meta-analysis. *Fertil Steril*. 2022;118(1):111-122.

34. Obeid R, Derbyshire E, Schön C. Association between Maternal Choline, Fetal Brain Development, and Child Neurocognition: Systematic Review and Meta-Analysis of Human Studies. *Adv Nutr*. 2022;13(6):2445-2457.

35. Irvine N, England-Mason G, Field CJ, Dewey D, Aghajafari F. Prenatal Folate and Choline Levels and Brain and Cognitive Development in Children: A Critical Narrative Review. *Nutrients*. 2022;14(2).

36. Johnson EJ. Role of lutein and zeaxanthin in visual and cognitive function throughout the lifespan. *Nutr Rev*. 2014;72(9):605-612.

37. Mahmassani HA, Switkowski KM, Scott TM, et al. Maternal Intake of Lutein and Zeaxanthin during Pregnancy Is Positively Associated with Offspring Verbal Intelligence and Behavior Regulation in Mid-Childhood in the Project Viva Cohort. *J Nutr*. 2021;151(3):615-627.

38. Cappellini MD, Santini V, Braxs C, Shander A. Iron metabolism and iron deficiency anemia in women. *Fertil Steril*. 2022;118(4):607-614.

39. Petraglia F, Dolmans MM. Iron deficiency anemia: Impact on women's reproductive health. *Fertil Steril*. 2022;118(4):605-606.

40. Institute of Medicine. 2001. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: The National Academies Press. https://doi.org/10.17226/10026.

41. Das J, Maitra A. Maternal DNA Methylation During Pregnancy: a Review. *Reprod Sci*. 2021;28(10):2758-2769.

42. Puig S, Ramos-Alonso L, Romero AM, Martínez-Pastor MT. The elemental role of iron in DNA synthesis and repair. *Metallomics*. 2017;9(11):1483-1500.

43. Singh AK, Kumar SL, Beniwal R, Mohanty A, Kushwaha B, Rao H. Local DNA synthesis is critical for DNA repair during oocyte maturation. *J Cell Sci*. 2021;134(19).

44. Kermi C, Aze A, Maiorano D. Preserving Genome Integrity During the Early Embryonic DNA Replication Cycles. *Genes (Basel)*. 2019;10(5).

45. Brannon PM, Taylor CL. Iron Supplementation during Pregnancy and Infancy: Uncertainties and Implications for Research and Policy. *Nutrients*. 2017;9(12).

46. Lakhal-Littleton S, Robbins PA. The interplay between iron and oxygen homeostasis with a particular focus on the heart. *J Appl Physiol (1985)*. 2017;123(4):967-973.

47. Stevens GA, Paciorek CJ, Flores-Urrutia MC, et al. National, regional, and global estimates of anaemia by severity in women and children for 2000-19: a pooled analysis of population-representative data. *Lancet Glob Health*. 2022;10(5):e627-e639.

48. Karami M, Chaleshgar M, Salari N, Akbari H, Mohammadi M. Global Prevalence of Anemia in Pregnant Women: A Comprehensive Systematic Review and Meta-Analysis. *Maternal and Child Health Journal*. 2022;26(7):1473-1487.

49. Georgieff MK. Iron deficiency in pregnancy. *Am J Obstet Gynecol*. 2020;223(4):516-524.

50. Fishman SM, Christian P, West KP. The role of vitamins in the prevention and control of anaemia. *Public Health Nutr*. 2000;3(2):125-150.

51. Karakochuk et al. (eds.) 2022. Nutritional Anemia. Nutrition and Health. Springer, 2nd ed.

52. Ritchie H, Roser M. Micronutrient Deficiency. Our World in Data. https://ourworldindata.org/micronutrient-deficiency#anemia-in-women-of-reproductive-age. Published 2017. Accessed February 10, 2023.

53. Georgsen M, Krog MC, Korsholm AS, et al. Serum ferritin level is inversely related to number of previous pregnancy losses in women with recurrent pregnancy loss. *Fertil Steril*. 2021;115(2):389-396.

54. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Iron intake and risk of ovulatory infertility. *Obstet Gynecol*. 2006;108(5):1145-1152.

55. Tonai S, Kawabata A, Nakanishi T, et al. Iron deficiency induces female infertile in order to failure of follicular development in mice. *J Reprod Dev*. 2020;66(5):475-483.

56. Hahn KA, Wesselink AK, Wise LA, et al. Iron Consumption Is Not Consistently Associated with Fecundability among North American and Danish Pregnancy Planners. *J Nutr*. 2019;149(9):1585-1595.

57. Abu-Ouf NM, Jan MM. The impact of maternal iron deficiency and iron deficiency anemia on child's health. *Saudi Med J*. 2015;36(2):146-149.

58. Geta TG, Gebremedhin S, Omigbodun AO. Prevalence and predictors of anemia among pregnant women in Ethiopia: Systematic review and meta-analysis. *PLoS One*. 2022;17(7):e0267005.

59. Taeubert MJ, de Prado-Bert P, Geurtsen ML, et al. Maternal iron status in early pregnancy and DNA methylation in offspring: an epigenome-wide meta-analysis. *Clin Epigenetics*. 2022;14(1):59.

60. Iglesias L, Canals J, Arija V. Effects of prenatal iron status on child neurodevelopment and behavior: A systematic review. *Crit Rev Food Sci Nutr*. 2018;58(10):1604-1614.

61. Iglesias-Vázquez L, Hernández-Martínez C, Voltas N, et al. Adapting prenatal iron supplementation to maternal needs results in optimal child neurodevelopment: a follow-up of the ECLIPSES Study. *BMC Pregnancy Childbirth*. 2022;22(1):710.

62. Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. *Cochrane Database Syst Rev*. 2015a;2015(7):Cd004736.

63. Peña-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. *Cochrane Database Syst Rev*. 2015b;2015(10):Cd009997.

64. Artym J, Zimecki M, Kruzel ML. Lactoferrin for Prevention and Treatment of Anemia and Inflammation in Pregnant Women: A Comprehensive Review. *Biomedicines*. 2021;9(8).

65. ACOG. ACOG Practice Bulletin No. 95: anemia in pregnancy. *Obstet Gynecol*. 2008;112(1):201-207.

66. Yip R PI, Cogswell M.E., McDonnell S.M., Bowman B.A., Grummer-Strawn L.M., Trowbridge F. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 1998;47(Rr-3):1-29.

67. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. https://www.who.int/publications/i/item/9789241549912. Published 2016. Accessed March 10, 2023.

68. EFSA Panel on Dietetic Products N, Allergies. Scientific Opinion on Dietary Reference Values for iron. *EFSA Journal*. 2015;13(10):4254.

69. Australia Government: Department of Health and Aged Care. Pregnancy Care Guidelines. Available at: https://www.health.gov.au/resources/pregnancy-care-guidelines/part-c-lifestyle-considerations/nutrition-and-physical-activity. Published 2020.

70. Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*. Washington, DC: The National Academies Press; 1998.

71. Wilson RD, O'Connor DL. Maternal folic acid and multivitamin supplementation: International clinical evidence with considerations for the prevention of folate-sensitive birth defects. *Prev Med Rep*. 2021;24:101617.

72. Bailey LB, Stover PJ, McNulty H, et al. Biomarkers of Nutrition for Development-Folate Review. *J Nutr*. 2015;145(7):1636s-1680s.

73. Kancherla V. Neural tube defects: a review of global prevalence, causes, and primary prevention. *Child's Nervous System*. 2023.

74. Kancherla V, Botto LD, Rowe LA, et al. Preventing birth defects, saving lives, and promoting health equity: an urgent call to action for universal mandatory food fortification with folic acid. *Lancet Glob Health*. 2022;10(7):e1053-e1057.

75. Rogers LM, Cordero AM, Pfeiffer CM, et al. Global folate status in women of reproductive age: a systematic review with emphasis on methodological issues. *Ann N Y Acad Sci*. 2018;1431(1):35-57.

76. Gaiday AN, Tussupkaliyev AB, Bermagambetova SK, et al. Effect of homocysteine on pregnancy: A systematic review. *Chem Biol Interact*. 2018;293:70-76.

77. World Health Organziation. WHO Guidelines Approved by the Guidelines Review Committee. In: *Guideline: Optimal Serum and Red Blood Cell Folate Concentrations in Women of Reproductive Age for Prevention of Neural Tube Defects*. Geneva: World Health Organization. Copyright © World Health Organization; 2015.

78. Ledowsky C, Steel A, Schloss J. Methylenetetrahydrofolate Reductase (MTHFR) genetic polymorphisms and the risk of infertility in couples accessing Assisted Reproductive technologies: a systematic review. *Advances in Integrative Medicine*. 2021;8(3):220-229.

79. Almekkawi AK, AlJardali MW, Daadaa HM, et al. Folate Pathway Gene Single Nucleotide Polymorphisms and Neural Tube Defects: A Systematic Review and Meta-Analysis. *J Pers Med*. 2022;12(10).

80. Nefic H, Mackic-Djurovic M, Eminovic I. The Frequency of the 677C>T and 1298A>C Polymorphisms in the Methylenetetrahydrofolate Reductase (MTHFR) Gene in the Population. *Med Arch*. 2018;72(3):164-169.

81. Frosst P, Blom HJ, Milos R, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet*. 1995;10(1):111-113.

82. Botto LD, Yang Q. 5, 10-Methylenetetrahydrofolate Reductase Gene Variants and Congenital Anomalies: A HuGE Review. *American Journal of Epidemiology*. 2000;151(9):862-877.

83. van der Put NMJ, Trijbels FJM, van den Heuvel LP, et al. Mutated methylenetetrahydrofolate reductase as a risk factor for spina bifida. *The Lancet*. 1995;346(8982):1070-1071.

84. Binia A, Contreras AV, Canizales-Quinteros S, Alonzo VA, Tejero ME, Silva-Zolezzi I. Geographical and ethnic distribution of single nucleotide polymorphisms within genes of the folate/homocysteine pathway metabolism. *Genes & Nutrition*. 2014;9(5):421.

85. Prinz-Langenohl R, Brämswig S, Tobolski O, et al. [6S]-5-methyltetrahydrofolate increases plasma folate more effectively than folic acid in women with the homozygous or wild-type 677C-->T polymorphism of methylenetetrahydrofolate reductase. *Br J Pharmacol*. 2009;158(8):2014-2021.

86. Konings EJ, Roomans HH, Dorant E, Goldbohm RA, Saris WH, van den Brandt PA. Folate intake of the Dutch population according to newly established liquid chromatography data for foods. *The American Journal of Clinical Nutrition*. 2001;73(4):765-776.

87. Lammi-Keefe CJ, Couch SC, Kirwan JP. *Handbook of nutrition and pregnancy*. Humana Press; 2018.

88. Gaskins AJ, Rich-Edwards JW, Hauser R, et al. Maternal prepregnancy folate intake and risk of spontaneous abortion and stillbirth. *Obstet Gynecol*. 2014;124(1):23-31.

89. Thaler CJ. Folate Metabolism and Human Reproduction. *Geburtshilfe Frauenheilkd*. 2014;74(9):845-851.

90. Czeizel AE, Métneki J, Dudás I. The effect of preconceptional multivitamin supplementation on fertility. *Int J Vitam Nutr Res*. 1996;66(1):55-58.

91. Westphal LM, Polan ML, Trant AS. Double-blind, placebo-controlled study of Fertilityblend: a nutritional supplement for improving fertility in women. *Clin Exp Obstet Gynecol*. 2006;33(4):205-208.

92. Ebisch IM, Thomas CM, Peters WH, Braat DD, Steegers-Theunissen RP. The importance of folate, zinc and antioxidants in the pathogenesis and prevention of subfertility. *Hum Reprod Update*. 2007;13(2):163-174.

93. Murto T, Skoog Svanberg A, Yngve A, et al. Folic acid supplementation and IVF pregnancy outcome in women with unexplained infertility. *Reproductive BioMedicine Online*. 2014;28(6):766-772.

94. Cirillo M, Fucci R, Rubini S, Coccia ME, Fatini C. 5-Methyltetrahydrofolate and Vitamin B12 Supplementation Is Associated with Clinical Pregnancy and Live Birth in Women Undergoing Assisted Reproductive Technology. *Int J Environ Res Public Health*. 2021;18(23).

95. Essmat A. Comparative Study between the Use of Regular Folic Acid Supplement versus the Use of L-Methyl Folate in Patients with Methyl Tetrahydrofolate Reductase (MTHFR) Gene Mutation with Recurrent Pregnancy Loss. *Open Journal of Obstetrics and Gynecology*. 2021;11:1104-1111.

96. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Folic Acid Supplementation for the Prevention of Neural Tube Defects: US Preventive Services Task Force Recommendation Statement. *Jama*. 2017;317(2):183-189.

97. Chen Z, Xing Y, Yu X, Dou Y, Ma D. Effect of Folic Acid Intake on Infant and Child Allergic Diseases: Systematic Review and Meta-Analysis. *Front Pediatr*. 2020;8:615406.

98. McGowan EC, Hong X, Selhub J, et al. Association Between Folate Metabolites and the Development of Food Allergy in Children. *J Allergy Clin Immunol Pract*. 2020;8(1):132-140.e135.

99. Bobrowski-Khoury N, Ramaekers VT, Sequeira JM, Quadros EV. Folate Receptor Alpha Autoantibodies in Autism Spectrum Disorders: Diagnosis, *Treatment and Prevention*. *J Pers Med*. 2021;11(8).

100. Hoxha B, Hoxha M, Domi E, et al. Folic Acid and Autism: A Systematic Review of the Current State of Knowledge. *Cells*. 2021;10(8).

101. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol*. 2005;106(5 Pt 1):1071-1083.

102. Jin X, Cheng Z, Yu X, Tao Q, Huang R, Wang S. Continuous supplementation of folic acid in pregnancy and the risk of perinatal depression-A meta-analysis. *J Affect Disord*. 2022;302:258-272.

103. De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. *Cochrane Database Syst Rev*. 2015;2015(12):Cd007950.

104. Viswanathan M, Treiman KA, Kish-Doto J, Middleton JC, Coker-Schwimmer EJL, Nicholson WK. Folic Acid Supplementation for the Prevention of Neural Tube Defects: An Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2017;317(2):190-203.

105. Henderson AM, Aleliunas RE, Loh SP, et al. l-5-Methyltetrahydrofolate Supplementation Increases Blood Folate Concentrations to a Greater Extent than Folic Acid Supplementation in Malaysian Women. *J Nutr*. 2018;148(6):885-890.

106. Lamers Y, Prinz-Langenohl R, Brämswig S, Pietrzik K. Red blood cell folate concentrations increase more after supplementation with [6S]-5-methyltetrahydrofolate than with folic acid in women of childbearing age. *Am J Clin Nutr*. 2006;84(1):156-161.

107. Schaefer E, Bieri G. A Randomized, Placebo-Controlled Trial in Women of Childbearing Age to Assess the Effect of Folic Acid and Methyl-Tetrahydrofolate on Erythrocyte Folate Levels. *Vitamins & Minerals*. 2016;05.

108. Troesch B, Demmelmair J, Gimpfl M, et al. Suitability and safety of L-5-methyltetrahydrofolate as a folate source in infant formula: A randomized-controlled trial. *PLoS One*. 2019;14(8):e0216790.

109. Wilson RD, Wilson RD, Audibert F, et al. Pre-conception Folic Acid and Multivitamin Supplementation for the Primary and Secondary Prevention of Neural Tube Defects and Other Folic Acid-Sensitive Congenital Anomalies. *J Obstet Gynaecol Can*. 2015;37(6):534-552.

110. American College of Obstetricians and Gynecologists. Neural tube defects. *Practice Bulletin No 187*. 2017;130:e279-90.

111. Australian Department of Health. Clinical Practice Guidelines: Pregnancy Care. In. Canberra: Australian Government Department of Health; 2020.

112. Watters C, Edmonds C, Rosner L, Sloss K, Leung P. A cost analysis of EPA and DHA in fish, supplements and foods. *J Nutr Food Sci*. 2012;2(8):159.

113. Chiu YH, Karmon AE, Gaskins AJ, et al. Serum omega-3 fatty acids and treatment outcomes among women undergoing assisted reproduction. *Hum Reprod*. 2018;33(1):156-165.

114. Colombo J, Jill Shaddy D, Kerling EH, Gustafson KM, Carlson SE. Docosahexaenoic acid (DHA) and arachidonic acid (ARA) balance in developmental outcomes. *Prostaglandins Leukot Essent Fatty Acids*. 2017;121:52-56.

115. Carlson SE, Colombo J. Docosahexaenoic Acid and Arachidonic Acid Nutrition in Early Development. *Adv Pediatr*. 2016;63(1):453-471.

116. Lepping RJ, Honea RA, Martin LE, et al. Long-chain polyunsaturated fatty acid supplementation in the first year of life affects brain function, structure, and metabolism at age nine years. *Dev Psychobiol*. 2019;61(1):5-16.

117. Nevins JEH, Donovan SM, Snetselaar L, et al. Omega-3 Fatty Acid Dietary Supplements Consumed During Pregnancy and Lactation and Child Neurodevelopment: A Systematic Review. *J Nutr*. 2021;151(11):3483-3494.

118. Zhang M-M, Zou Y, Li S-M, et al. The efficacy and safety of omega-3 fatty acids on depressive symptoms in perinatal women: a meta-analysis of randomized placebo-controlled trials. *Translational Psychiatry*. 2020;10(1):193.

119. Best KP, Gibson RA, Makrides M. ISSFAL statement number 7 - Omega-3 fatty acids during pregnancy to reduce preterm birth. *Prostaglandins Leukot Essent Fatty Acids*. 2022;186:102495.

120. Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. *Cochrane Database Syst Rev*. 2018;11(11):Cd003402.

121. Muskiet FA, Fokkema MR, Schaafsma A, Boersma ER, Crawford MA. Is docosahexaenoic acid (DHA) essential? Lessons from DHA status regulation, our ancient diet, epidemiology and randomized controlled trials. *J Nutr*. 2004;134(1):183-186.

122. Koletzko B. Prenatal supply of docosahexaenoic acid (DHA): should we be worried? *J Perinat Med*. 2008;36(3):265-267; author reply 268-269.

123. Glaser C, Heinrich J, Koletzko B. Role of FADS1 and FADS2 polymorphisms in polyunsaturated fatty acid metabolism. *Metabolism*. 2010;59(7):993-999.

124. Stark KD, Van Elswyk ME, Higgins MR, Weatherford CA, Salem N, Jr. Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults. *Prog Lipid Res*. 2016;63:132-152.

125. Simopoulos AP. Omega-6/Omega-3 Essential Fatty Acid Ratio and Chronic Diseases. *Food Reviews International*. 2004;20(1):77-90.

126. Wang R, Feng Y, Chen J, Chen Y, Ma F. Association between polyunsaturated fatty acid intake and infertility among American women aged 20-44 years. *Front Public Health*. 2022;10:938343.

127. Moran LJ, Tsagareli V, Noakes M, Norman R. Altered Preconception Fatty Acid Intake Is Associated with Improved Pregnancy Rates in Overweight and Obese Women Undertaking in Vitro Fertilisation. *Nutrients*. 2016;8(1).

128. Stanhiser J, Jukic AMZ, McConnaughey DR, Steiner AZ. Omega-3 fatty acid supplementation and fecundability. *Hum Reprod*. 2022;37(5):1037-1046.

129. Al-Alousi T. A., Al-Allak M. M. A., Aziz A. A., et al. The Effect of Omega-3 on the Number of Retrieved Ova, Fertilization Rate, and Embryo Grading in Subfertile Women Undergoing Intracytoplasmic Sperm Injection. *Biomed Pharmacol J*. 2018;11(4).

130. Trop-Steinberg S, Heifetz EM, Azar Y, Kafka I, Weintraub A, Gal M. Omega-3 Intake Improves Clinical Pregnancy Rate in Polycystic Ovary Syndrome Patients: A Double-Blind, Randomized Study. *Isr Med Assoc J*. 2023;25(2):131-136.

131. Larqué E, Demmelmair H, Gil-Sánchez A, et al. Placental transfer of fatty acids and fetal implications. *The American Journal of Clinical Nutrition*. 2011;94(suppl_6):1908S-1913S.

132. Svennerholm L. Distribution and fatty acid composition of phosphoglycerides in normal human brain. *J Lipid Res*. 1968;9(5):570-579.

133. Lin PY, Chang CH, Chong MF, Chen H, Su KP. Polyunsaturated Fatty Acids in Perinatal Depression: A Systematic Review and Meta-analysis. *Biol Psychiatry*. 2017;82(8):560-569.

134. Ciesielski TH, Bartlett J, Williams SM. Omega-3 polyunsaturated fatty acid intake norms and preterm birth rate: a cross-sectional analysis of 184 countries. *BMJ Open*. 2019;9(4):e027249.

135. Ciesielski TH, Williams SM. Low Omega-3 intake is associated with high rates of depression and preterm birth on the country level. *Sci Rep*. 2020;10(1):19749.

136. Olsen SF, Secher NJ. Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study. *Bmj*. 2002;324(7335):447.

137. Leventakou V, Roumeliotaki T, Martinez D, et al. Fish intake during pregnancy, fetal growth, and gestational length in 19 European birth cohort studies. *Am J Clin Nutr*. 2014;99(3):506-516.

138. Wang L, Fu Z, Deng W, Zhu S, Zhang C, Zhang W. Maternal fish and shellfish consumption and preterm birth: a retrospective study in urban China. *Br J Nutr*. 2022;128(4):684-692.

139. Simmonds LA, Sullivan TR, Skubisz M, et al. Omega-3 fatty acid supplementation in pregnancy-baseline omega-3 status and early preterm birth: exploratory analysis of a randomised controlled trial. *Bjog*. 2020;127(8):975-981.

140. Olsen SF, Halldorsson TI, Thorne-Lyman AL, et al. Plasma Concentrations of Long Chain N-3 Fatty Acids in Early and Mid-Pregnancy and Risk of Early Preterm Birth. *EBioMedicine*. 2018;35:325-333.

141. Makrides M, Best K, Yelland L, et al. A Randomized Trial of Prenatal n-3 Fatty Acid Supplementation and Preterm Delivery. *N Engl J Med*. 2019;381(11):1035-1045.

142. Carlson SE, Gajewski BJ, Valentine CJ, et al. Early and late preterm birth rates in participants adherent to randomly assigned high dose docosahexaenoic acid (DHA) supplementation in pregnancy. *Clin Nutr*. 2023;42(2):235-243.

143. Simmonds LA, Yelland LN, Best KP, Liu G, Gibson RA, Makrides M. Translating n-3 polyunsaturated fatty acid status from whole blood to plasma and red blood cells during pregnancy: Translating n-3 status across blood fractions in pregnancy. *Prostaglandins Leukot Essent Fatty Acids*. 2022;176:102367.

144. Christifano DN, Crawford SA, Lee G, et al. Docosahexaenoic acid (DHA) intake estimated from a 7-question survey identifies pregnancies most likely to benefit from high-dose DHA supplementation. *Clin Nutr ESPEN*. 2023;53:93-99.

145. Carlson SE, Colombo J, Gajewski BJ, et al. DHA supplementation and pregnancy outcomes. *Am J Clin Nutr*. 2013;97(4):808-815.

146. Global Organization for EPA and DHA Omega-3 (GOED). Global recommendations for EPA and DHA intake. https://www.issfal.org/goed-recommendations-for-epa-dha. Published 2019. Accessed December 12, 2022.

147. Jia X, Pakseresht M, Wattar N, et al. Women who take n-3 long-chain polyunsaturated fatty acid supplements during pregnancy and lactation meet the recommended intake. *Appl Physiol Nutr Metab*. 2015;40(5):474-481.

148. Zimmer M, Sieroszewski P, Oszukowski P, Huras H, Fuchs T, Pawlosek A. Polish Society of Gynecologists and Obstetricians recommendations on supplementation during pregnancy. *Ginekol Pol*. 2020;91(10):644-653.

149. National Institute of Health Office of Dietary Supplements. Vitamin D: Fact Sheet for Health Professionals. https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/. Updated August 12, 2022. Accessed February 10, 2023.

150. Mansur JL, Oliveri B, Giacoia E, Fusaro D, Costanzo PR. Vitamin D: Before, during and after Pregnancy: Effect on Neonates and Children. *Nutrients*. 2022;14(9).

151. Tian M, Zeng S, Cai S, et al. 25(OH)VitD and human endocrine and functional fertility parameters in women undergoing IVF/ICSI. *Front Endocrinol (Lausanne)*. 2022;13:986848.

152. Meng X, Zhang J, Wan Q, et al. Influence of Vitamin D supplementation on reproductive outcomes of infertile patients: a systematic review and meta-analysis. *Reprod Biol Endocrinol*. 2023;21(1):17.

153. Aguilar-Cordero MJ, Lasserrot-Cuadrado A, Mur-Villar N, León-Ríos XA, Rivero-Blanco T, Pérez-Castillo IM. Vitamin D, preeclampsia and prematurity: A systematic review and meta-analysis of observational and interventional studies. *Midwifery*. 2020;87:102707.

154. Saraf R, Morton SM, Camargo CA, Jr., Grant CC. Global summary of maternal and newborn vitamin D status - a systematic review. *Matern Child Nutr*. 2016;12(4):647-668.

155. Hansen KE, Johnson RE, Chambers KR, et al. Treatment of Vitamin D Insufficiency in Postmenopausal Women: A Randomized Clinical Trial. *JAMA Intern Med*. 2015;175(10):1612-1621.

156. Cianferotti L, Marcocci C. Subclinical vitamin D deficiency. *Best Pract Res Clin Endocrinol Metab*. 2012;26(4):523-537.

157. Pilz S, Zittermann A, Obeid R, et al. The Role of Vitamin D in Fertility and during Pregnancy and Lactation: A Review of Clinical Data. *Int J Environ Res Public Health*. 2018;15(10).

158. Muscogiuri G, Altieri B, de Angelis C, et al. Shedding new light on female fertility: The role of vitamin D. *Rev Endocr Metab Disord*. 2017;18(3):273-283.

159. Chu J, Gallos I, Tobias A, Tan B, Eapen A, Coomarasamy A. Vitamin D and assisted reproductive treatment outcome: a systematic review and meta-analysis. *Hum Reprod*. 2018;33(1):65-80.

160. Andersen LB, Jørgensen JS, Jensen TK, et al. Vitamin D insufficiency is associated with increased risk of first-trimester miscarriage in the Odense Child Cohort. *Am J Clin Nutr*. 2015;102(3):633-638.

161. Chen C, Wang S, Zhang C, et al. Association between serum vitamin D level during pregnancy and recurrent spontaneous abortion: A systematic review and meta-analysis. *Am J Reprod Immunol*. 2022;88(3):e13582.

162. Zhou X, Wu X, Luo X, et al. Effect of Vitamin D Supplementation on In Vitro Fertilization Outcomes: A Trial Sequential Meta-Analysis of 5 Randomized Controlled Trials. *Front Endocrinol (Lausanne)*. 2022;13:852428.

163. Zhang H, Wang S, Tuo L, et al. Relationship between Maternal Vitamin D Levels and Adverse Outcomes. *Nutrients*. 2022;14(20).

164. Yin WJ, Tao RX, Hu HL, et al. The association of vitamin D status and supplementation during pregnancy with gestational diabetes mellitus: a Chinese prospective birth cohort study. *Am J Clin Nutr*. 2020;111(1):122-130.

165. Hu L, Zhang Y, Wang X, et al. Maternal Vitamin D Status and Risk of Gestational Diabetes: a Meta-Analysis. *Cell Physiol Biochem*. 2018;45(1):291-300.

166. Yuan Y, Tai W, Xu P, et al. Association of maternal serum 25-hydroxyvitamin D concentrations with risk of preeclampsia: a nested case-control study and meta-analysis. *J Matern Fetal Neonatal Med*. 2021;34(10):1576-1585.

167. McDonnell SL, Baggerly KA, Baggerly CA, et al. Maternal 25(OH)D concentrations ≥40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. *PLoS One*. 2017;12(7):e0180483.

168. Zhao R, Zhou L, Wang S, Yin H, Yang X, Hao L. Effect of maternal vitamin D status on risk of adverse birth outcomes: a systematic review and dose-response meta-analysis of observational studies. *Eur J Nutr*. 2022;61(6):2881-2907.

169. Chen Y, Zhu B, Wu X, Li S, Tao F. Association between maternal vitamin D deficiency and small for gestational age: evidence from a meta-analysis of prospective cohort studies. *BMJ Open*. 2017;7(8):e016404.

170. Palacios C, Kostiuk LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews*. 2019(7).

171. Irwinda R, Hiksas R, Lokeswara AW, Wibowo N. Vitamin D supplementation higher than 2000 IU/day compared to lower dose on maternal-fetal outcome: Systematic review and meta-analysis. *Womens Health (Lond)*. 2022;18:17455057221111066.

172. Liu Y, Ding C, Xu R, et al. Effects of vitamin D supplementation during pregnancy on offspring health at birth: A meta-analysis of randomized controlled trails. *Clin Nutr*. 2022;41(7):1532-1540.

173. Gázquez A, Sánchez-Campillo M, Barranco A, et al. Calcifediol During Pregnancy Improves Maternal and Fetal Availability of Vitamin D Compared to Vitamin D3 in Rats and Modifies Fetal Metabolism. *Front Nutr*. 2022;9:871632.

174. Cashman KD, Seamans KM, Lucey AJ, et al. Relative effectiveness of oral 25-hydroxyvitamin D3 and vitamin D3 in raising wintertime serum 25-hydroxyvitamin D in older adults. *Am J Clin Nutr*. 2012;95(6):1350-1356.

175. Vaes AMM, Tieland M, de Regt MF, Wittwer J, van Loon LJC, de Groot L. Dose-response effects of supplementation with calcifediol on serum 25-hydroxyvitamin D status and its metabolites: A randomized controlled trial in older adults. *Clin Nutr*. 2018;37(3):808-814.

176. Quesada-Gomez JM, Bouillon R. Is calcifediol better than cholecalciferol for vitamin D supplementation? *Osteoporos Int*. 2018;29(8):1697-1711.

177. Pérez-Castrillon JL, Usategui-Martín R, Pludowski P. Treatment of Vitamin D Deficiency with Calcifediol: Efficacy and Safety Profile and Predictability of Efficacy. *Nutrients*. 2022;14(9).

178. Navarro-Valverde C, Sosa-Henríquez M, Alhambra-Expósito MR, Quesada-Gómez JM. Vitamin D(3) and calcidiol are not equipotent. *J Steroid Biochem Mol Biol*. 2016;164:205-208.

179. American College of Obstetricians and Gynecologists (ACOG). ACOG Committee Opinion No. 495: Vitamin D: Screening and supplementation during pregnancy. *Obstet Gynecol*. 2011;118(1):197-198.

180. Hanson MA, Bardsley A, De-Regil LM, et al. The International Federation of Gynecology and Obstetrics (FIGO) recommendations on adolescent, preconception, and maternal nutrition: "Think Nutrition First". *Int J Gynaecol Obstet*. 2015;131 Suppl 4:S213-253.

181. Wallace TC, Blusztajn JK, Caudill MA, et al. Choline: The Underconsumed and Underappreciated Essential Nutrient. *Nutr Today*. 2018;53(6):240-253.

182. Zeisel SH. Choline: critical role during fetal development and dietary requirements in adults. *Annu Rev Nutr*. 2006b;26:229-250.

183. Nyaradi A, Li J, Hickling S, Foster J, Oddy WH. The role of nutrition in children's neurocognitive development, from pregnancy through childhood. *Front Hum Neurosci*. 2013;7:97.

184. Bailey RL, Pac SG, Fulgoni VL, 3rd, Reidy KC, Catalano PM. Estimation of Total Usual Dietary Intakes of Pregnant Women in the United States. *JAMA Netw Open*. 2019;2(6):e195967.

185. Derbyshire E, Obeid R, Schön C. Habitual Choline Intakes across the Childbearing Years: A Review. *Nutrients*. 2021;13(12).

186. Hartge DR, Gembicki M, Rody A, Weichert J. Neural Tube Defects in Embryonic Life: Lessons Learned From 340 Early Pregnancy Failures. *J Ultrasound Med*. 2018;37(12):2841-2847.

187. Zhan X, Fletcher L, Dingle S, et al. Choline supplementation influences ovarian follicular development. *FBL*. 2021;26(12):1525-1536.

188. Sun L, Hu W, Liu Q, et al. Metabonomics reveals plasma metabolic changes and inflammatory marker in polycystic ovary syndrome patients. *J Proteome Res*. 2012;11(5):2937-2946.

189. Ersahin AA, Çalışkan E. Clomiphene citrate changes metabolite content of follicular fluid of PCOS women. *Eur Rev Med Pharmacol Sci*. 2018;22(13):4359-4362.

190. Derbyshire E, Obeid R. Choline, Neurological Development and Brain Function: A Systematic Review Focusing on the First 1,000 Days. *Nutrients*. 2020;12(6).

191. Shaw GM, Carmichael SL, Yang W, Selvin S, Schaffer DM. Periconceptional dietary intake of choline and betaine and neural tube defects in offspring. *Am J Epidemiol*. 2004;160(2):102-109.

192. Shaw GM, Finnell RH, Blom HJ, et al. Choline and risk of neural tube defects in a folate-fortified population. *Epidemiology*. 2009;20(5):714-719.

193. Wu BT, Dyer RA, King DJ, Richardson KJ, Innis SM. Early second trimester maternal plasma choline and betaine are related to measures of early cognitive development in term infants. *PLoS One*. 2012;7(8):e43448.

194. Bahnfleth CL, Strupp BJ, Caudill MA, Canfield RL. Prenatal choline supplementation improves child sustained attention: A 7-year follow-up of a randomized controlled feeding trial. *Faseb j*. 2022;36(1):e22054.

195. Boeke CE, Gillman MW, Hughes MD, Rifas-Shiman SL, Villamor E, Oken E. Choline intake during pregnancy and child cognition at age 7 years. *Am J Epidemiol*. 2013;177(12):1338-1347.

196. Klatt KC, McDougall MQ, Malysheva OV, et al. Prenatal choline supplementation improves biomarkers of maternal docosahexaenoic acid (DHA) status among pregnant participants consuming supplemental DHA: a randomized controlled trial. *Am J Clin Nutr*. 2022;116(3):820-832.

197. Caudill MA, Strupp BJ, Muscalu L, Nevins JEH, Canfield RL. Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study. *Faseb j*. 2018;32(4):2172-2180.

198. Ross RG, Hunter SK, McCarthy L, et al. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. *Am J Psychiatry*. 2013;170(3):290-298.

199. Cheatham CL, Goldman BD, Fischer LM, da Costa KA, Reznick JS, Zeisel SH. Phosphatidylcholine supplementation in pregnant women consuming moderate-choline diets does not enhance infant cognitive function: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr*. 2012;96(6):1465-1472.

200. Tee ES. Carotenoids and retinoids in human nutrition. *Crit Rev Food Sci Nutr*. 1992;31(1-2):103-163.

201. Rao AV, Rao LG. Carotenoids and human health. *Pharmacological Research*. 2007;55(3):207-216.

202. Health NIo. Vitamin A and Carotenoids - Health Professional Fact Sheet. https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/. Updated June 15, 2022. Accessed March 15, 2023.

203. Watson PE, McDonald BW. Seasonal variation of nutrient intake in pregnancy: effects on infant measures and possible influence on diseases related to season of birth. *Eur J Clin Nutr*. 2007;61(11):1271-1280.

204. Zielińska MA, Wesołowska A, Pawlus B, Hamułka J. Health Effects of Carotenoids during Pregnancy and Lactation. *Nutrients*. 2017;9(8).

205. Brantsaeter AL, Haugen M, Rasmussen SE, Alexander J, Samuelsen SO, Meltzer HM. Urine flavonoids and plasma carotenoids in the validation of fruit, vegetable and tea intake during pregnancy in the Norwegian Mother and Child Cohort Study (MoBa). *Public Health Nutr*. 2007;10(8):838-847.

206. Institute of Medicine. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: The National Academies Press; 2006.

207. Li Z, Chen J, Zhang D. Association between dietary carotenoid intakes and hypertension in adults: National Health and Nutrition Examination Survey 2007–2014. *Journal of Hypertension*. 2019;37(12):2371-2379.

208. Böhm V, Lietz G, Olmedilla-Alonso B, et al. From carotenoid intake to carotenoid blood and tissue concentrations – implications for dietary intake recommendations. *Nutrition Reviews*. 2020;79(5):544-573.

209. Mumford SL, Browne RW, Schliep KC, et al. Serum Antioxidants Are Associated with Serum Reproductive Hormones and Ovulation among Healthy Women. *J Nutr*. 2016;146(1):98-106.

210. Polak G, Kozioł-Montewka M, Gogacz M, Błaszkowska I, Kotarski J. Total antioxidant status of peritoneal fluid in infertile women. *Eur J Obstet Gynecol Reprod Biol*. 2001;94(2):261-263.

211. Fenkci V, Fenkci S, Yilmazer M, Serteser M. Decreased total antioxidant status and increased oxidative stress in women with polycystic ovary syndrome may contribute to the risk of cardiovascular disease. *Fertil Steril*. 2003;80(1):123-127.

212. Ruder EH, Hartman TJ, Reindollar RH, Goldman MB. Female dietary antioxidant intake and time to pregnancy among couples treated for unexplained infertility. *Fertil Steril*. 2014;101(3):759-766.

213. Kim K, Schisterman EF, Silver RM, et al. Shorter Time to Pregnancy With Increasing Preconception Carotene Concentrations Among Women With 1-2 Previous Pregnancy Losses. *Am J Epidemiol*. 2018;187(9):1907-1915.

214. Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Pre-eclampsia: pathogenesis, novel diagnostics and therapies. *Nat Rev Nephrol*. 2019;15(5):275-289.

215. Kang T, Liu Y, Chen X, et al. Dietary carotenoid intake and risk of developing preeclampsia: a hospital-based case–control study. *BMC Pregnancy and Childbirth*. 2022;22(1):427.

216. Serdar Z, Gür E, Colakoethullarý M, Develioethlu O, Sarandöl E. Lipid and protein oxidation and antioxidant function in women with mild and severe preeclampsia. *Arch Gynecol Obstet*. 2003;268(1):19-25.

217. Yusuf H, Subih HS, Obeidat BS, Sharkas G. Associations of macro and micronutrients and antioxidants intakes with preeclampsia: A case-control study in Jordanian pregnant women. *Nutr Metab Cardiovasc Dis*. 2019;29(5):458-466.

218. Thoene M, Anderson-Berry A, Van Ormer M, et al. Quantification of Lutein + Zeaxanthin Presence in Human Placenta and Correlations with Blood Levels and Maternal Dietary Intake. *Nutrients*. 2019;11(1):134.

219. Rubin LP, Chan GM, Barrett-Reis BM, et al. Effect of carotenoid supplementation on plasma carotenoids, inflammation and visual development in preterm infants. *J Perinatol*. 2012;32(6):418-424.

220. Lai JS, Veetil VO, Lanca C, et al. Maternal Lutein and Zeaxanthin Concentrations in Relation to Offspring Visual Acuity at 3 Years of Age: The GUSTO Study. *Nutrients*. 2020;12(2).

221. Vishwanathan R, Kuchan MJ, Sen S, Johnson EJ. Lutein and preterm infants with decreased concentrations of brain carotenoids. *J Pediatr Gastroenterol Nutr*. 2014;59(5):659-665.

222. Gazzolo D, Picone S, Gaiero A, et al. Early Pediatric Benefit of Lutein for Maturing Eyes and Brain-An Overview. *Nutrients*. 2021;13(9).

223. Victora CG, Bahl R, Barros AJ, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet*. 2016;387(10017):475-490.

224. Hammond BR, Jr., Renzi LM. Carotenoids. *Adv Nutr*. 2013;4(4):474-476.

225. Sifuentes-Franco S, Sánchez-Macías DC, Carrillo-Ibarra S, Rivera-Valdés JJ, Zuñiga LY, Sánchez-López VA. Antioxidant and Anti-Inflammatory Effects of Coenzyme Q10 Supplementation on Infectious Diseases. *Healthcare* (Basel). 2022;10(3).

226. National Institutes of Health NCfCaIH. Coenzyme Q10. https://www.nccih.nih.gov/health/coenzyme-q10. Updated January 2019. Accessed February 14, 2023.

227. Xu Y, Nisenblat V, Lu C, et al. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. *Reprod Biol Endocrinol*. 2018;16(1):29.

228. Ben-Meir A, Burstein E, Borrego-Alvarez A, et al. Coenzyme Q10 restores oocyte mitochondrial function and fertility during reproductive aging. *Aging Cell*. 2015;14(5):887-895.

229. Florou P, Anagnostis P, Theocharis P, Chourdakis M, Goulis DG. Does coenzyme Q(10) supplementation improve fertility outcomes in women undergoing assisted reproductive technology procedures? A systematic review and meta-analysis of randomized-controlled trials. *J Assist Reprod Genet*. 2020;37(10):2377-2387.

230. Alahmar AT, Calogero AE, Sengupta P, Dutta S. Coenzyme Q10 Improves Sperm Parameters, Oxidative Stress Markers and Sperm DNA Fragmentation in Infertile Patients with Idiopathic Oligoasthenozoospermia. *World J Mens Health*. 2021;39(2):346-351.

231. Ahmadi S, Bashiri R, Ghadiri-Anari A, Nadjarzadeh A. Antioxidant supplements and semen parameters: An evidence based review. *Int J Reprod Biomed*. 2016;14(12):729-736.

232. Thornburgh S, Gaskins AJ. B vitamins, polycystic ovary syndrome, and fertility. *Curr Opin Endocrinol Diabetes Obes*. 2022;29(6):554-559.

233. Bennett M. Vitamin B12 deficiency, infertility and recurrent fetal loss. *J Reprod Med*. 2001;46(3):209-212.

234. Gaskins AJ, Chiu YH, Williams PL, et al. Association between serum folate and vitamin B-12 and outcomes of assisted reproductive technologies. *Am J Clin Nutr*. 2015;102(4):943-950.

235. Banihani SA. Vitamin B(12) and Semen Quality. *Biomolecules*. 2017;7(2).

236. Gambioli R, Forte G, Buzzaccarini G, Unfer V, Laganà AS. Myo-Inositol as a Key Supporter of Fertility and Physiological Gestation. *Pharmaceuticals (Basel)*. 2021;14(6).

237. Mendoza N, Losa F, Palacios S. Strategy to improve the female fertility in the general gynecologist's office: use of a nutritional supplement based on myo-inositol/D-chiro-inositol and antioxidants. *Gynecol Endocrinol*. 2022;38(4):275-278.

238. Colazingari S, Treglia M, Najjar R, Bevilacqua A. The combined therapy myo-inositol plus D-chiro-inositol, rather than D-chiro-inositol, is able to improve IVF outcomes: results from a randomized controlled trial. *Arch Gynecol Obstet*. 2013;288(6):1405-1411.

239. Regidor PA, Schindler AE, Lesoine B, Druckman R. Management of women with PCOS using myo-inositol and folic acid. New clinical data and review of the literature. *Horm Mol Biol Clin Investig*. 2018;34(2).

240. Vazquez-Levin MH, Verón GL. Myo-inositol in health and disease: its impact on semen parameters and male fertility. *Andrology*. 2020;8(2):277-298.

241. Boitani C, Puglisi R. Selenium, a key element in spermatogenesis and male fertility. *Adv Exp Med* Biol. 2008;636:65-73.

242. Ahsan U, Kamran Z, Raza I, et al. Role of selenium in male reproduction - a review. *Anim Reprod Sci*. 2014;146(1-2):55-62.

243. Montanino Oliva M, Minutolo E, Lippa A, Iaconianni P, Vaiarelli A. Effect of Myoinositol and Antioxidants on Sperm Quality in Men with Metabolic Syndrome. *Int J Endocrinol*. 2016;2016:1674950.

244. European Food Safety Authority. Dietary reference values for nutrients: Summary report. In:2017:92.

Acknowledgements:

Sarah Staskiewicz, RDN and the Cultivate: Nutrition Content and Strategy agency provided planning, conceptualization, medical writing, and editing for this publication.