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2023

State of Perinatal Nutrition

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Needed Perspective

The unequivocal evidence which has proven that nutrition can shape outcomes for maternal and child health cannot be ignored. The profound role of proper nutrition in sensitive and malleable windows of opportunity impacts not just immediate pregnancy experience and birth outcomes, but fertility, susceptibility, resilience, and health trajectories over the lifetime of mom, baby and future generations. ¹ This evidence must be acknowledged and accepted, such that it is ubiquitously integrated into clinical practice. A shift in the status quo of perinatal nutrition to acknowledge what is known must be accompanied by crucial investments in holistic perinatal support and high-quality research which assist to advance the understanding of the optimal perinatal nutritional paradigm. This shift in focus must be contextualized to optimize nutritional status in the overall lifespan as well as in sensitive gestational and postnatal windows which require individualized and evidence centered support. ²

Nutrient needs increase during pregnancy for almost all micronutrients and certain macronutrient forms, reflected in the nutrient reference values outlined by public health organizations and government agencies on a global scale.³ Unfortunately, harmonized and comprehensive guidance regarding perinatal nutritional requirements and care for women are grossly lacking.¹ While the critical function and investigation of optimal nutrition during the perinatal period has received limited consideration historically from health professionals spanning researchers to policy shaping organizations; Recent decades have been characterized by public urgency and strides in research which have contributed substantially to the knowledge base regarding the roles and needs for optimized nutrition in perinatal periods.^{4,5} However, there exist constant evolutions in our understanding of optimal nutrition and critical gaps in the evidence regarding perinatal nutrition spanning personalized needs, assessments, support, and care frameworks.⁶ Not to mention, the need to study constant interactions among these factors with biological, genetic, environmental, and societal factors and exposures. Pair all of this with a glaring lack of integration of what is already known into harmonized clinical practice, and we land here - a point of critical dysfunction in the perinatal nutritional paradigm, with women and children paying a steep price.

The integration and mobilization of the evidence to support individuals from the standpoint of optimized nutrition has the power to shift the transgenerational health balance towards longer and healthier lifespans. ² This requires coordinated efforts by external changemakers and integrated perinatal support to champion and empower intrinsic capacity in the spirit of promoting radical shifts in the current nutritional care model towards optimal nutrition and health. This is no easy task. This approach requires research, policy, and practice to acknowledge the primacy of interventions which aim to understand needs and support optimal nutrient provision throughout the preconception life span, and to build upon this foundation by prioritizing key perinatal windows with specific requirements and therapeutic touchpoints that must be met to foster generational health.⁶ Herein, we aim to outline the accumulated evidence which signals the pivotal role of perinatal nutrition and Needed's comprehensive approach to advance the evidence and spark large-scale mobilization in efforts to change the current perinatal nutrition paradigm.

Quotes from Needed collaborators in support of this perspective

Dr. Leslie Stone, OB-GYN applying nutrition interventions in a 50% Medicaid setting:

“Needed presents powerful and convincing evidence that our perinatal outcomes are worsening and are directly tied to diet and lifestyle, with generational impact. The time for change is now to remove institutional obstacles that have kept quality investigation of the perinatal time period off limits.”

Dr. Ari Calhoun, perinatal and pediatric Naturopathic Doctor and Certified Functional Medicine Practitioner:

“As a Naturopathic Doctor specializing in pediatric brain development, I see the tremendous impact that mom’s nutritional status and environmental exposures during pregnancy can have on a child’s cognitive trajectory. This paper identifies important areas of research that have been underappreciated in perinatal care. We have much more to learn, but we’re taking leaps in the right direction.”

Dr. Leah Gordon, fertility-focused Naturopathic Doctor and Certified Functional Medicine Practitioner:

“As a Naturopathic Doctor and fertility specialist, I cannot be more thrilled that Needed is diving in deep to explore the

perinatal nutritional paradigm in a truly meaningful way. I see so much opportunity for improved pregnancy outcomes with a greater focus on proper nutrition, starting in the preconception period, and honestly it's just been such a missed opportunity in the current standard of care.”

Emily Stone Rydbom, certified nutrition consultant, board-certified holistic nutritionist, and certified nutrition professional: “Since 2010, I have had the honor of working in the field of perinatal nutrition, creating & applying a perinatal program in both clinical and research settings to some of the most vulnerable OB populations. During the past decade, it has become evidently clear and irrefutable that if we indeed desire to reverse chronic disease, impact mental health & well-being, and improve generational health, we must start at the beginning of the lifespan. Integrating nutrition care in the perinatal time period can no longer be an afterthought, it is Needed. Needed’s mission to scale personalized and tailored maternal nutrition care for all mothers is the optimal way forward.”

Ryan Woodbury, Needed co-founder / Co-CEO and certified holistic nutritionist: “As a mother and trained nutritionist, I am incredibly passionate about making a radical impact to improve the integration of nutritional care into the current pregnancy care paradigm. We set out to aggregate and present undeniable evidence that nutrition changes pregnancy outcomes. We are now more convinced than ever that a change in the status quo is needed to improve health outcomes for mom, baby and future generations.”

Aletta Mayorga, Needed VP of R&D and Registered Dietitian: “As a mother and Registered Dietitian, I am absolutely convinced that nutrition has a tremendous impact in all life stages, but particularly during pregnancy and breastfeeding. Unfortunately, nutrition messaging can be inconsistent, often misleading, and most women simply aren’t getting the nutrition they need to optimize their health and wellbeing. I am honored to be a part of an effort to make a difference.”

Samantha Fessler, Doctoral Candidate in nutrition: “As a PhD Candidate in Nutrition, my research focuses on dietary supplement strategies as powerful tools to augment health outcomes through the lens of systems biology. Nutritional exposures are vital to shaping intergenerational health outcomes, and perinatal periods are profound windows which are particularly sensitive to nutritional influence. Unfortunately, we know without dietary supplementation many women will not be optimally nourished during these timeframes and it is thrilling to be a part of this effort to build a bridge to translate contemporary research to women and place them in control of their health and the health of future generations!”

Need for additional dietary supplementation beyond dietary consumption:

Emphasis on the perinatal period

It is well categorized that while epigenetic alterations occur over the lifetime, perinatal periods are pivotal timeframes in which biological systems are particularly sensitive to environmental exposures which can shape development and risk for non-communicable conditions across the lifespan and may persist across multiple generations.⁷ The developmental origins of health and disease (DOHaD) concept derives from the research by David Barker and colleagues in 1986 suggesting that early life undernutrition may increase the risk for chronic diseases typically linked with wealth, in later life.⁸ This was based on the observations that heart disease mortality rates in England and Wales between 1968 to 1978 were associated with infant mortality between 1921 to 1925.⁸ Moreover, areas of low-income had elevated rates of infant mortality and heart disease. This concept has been fortified by consistent data from famine and cohort studies, such as the Dutch Hunger Winter studies examining the starvation experienced under German occupation in World War II, which provided compelling evidence regarding how extreme nutritional restriction in utero influences lifelong health outcomes.⁹ The impacts of famine experienced by women during gestation, echoed into the lives of the offspring exposed to such nutrient restriction in utero, who experienced increased risk for chronic disease throughout the lifespan.^{10–13} Thus, it is imperative to intervene well before these critical windows of opportunity, to create a framework for generational health resilience.

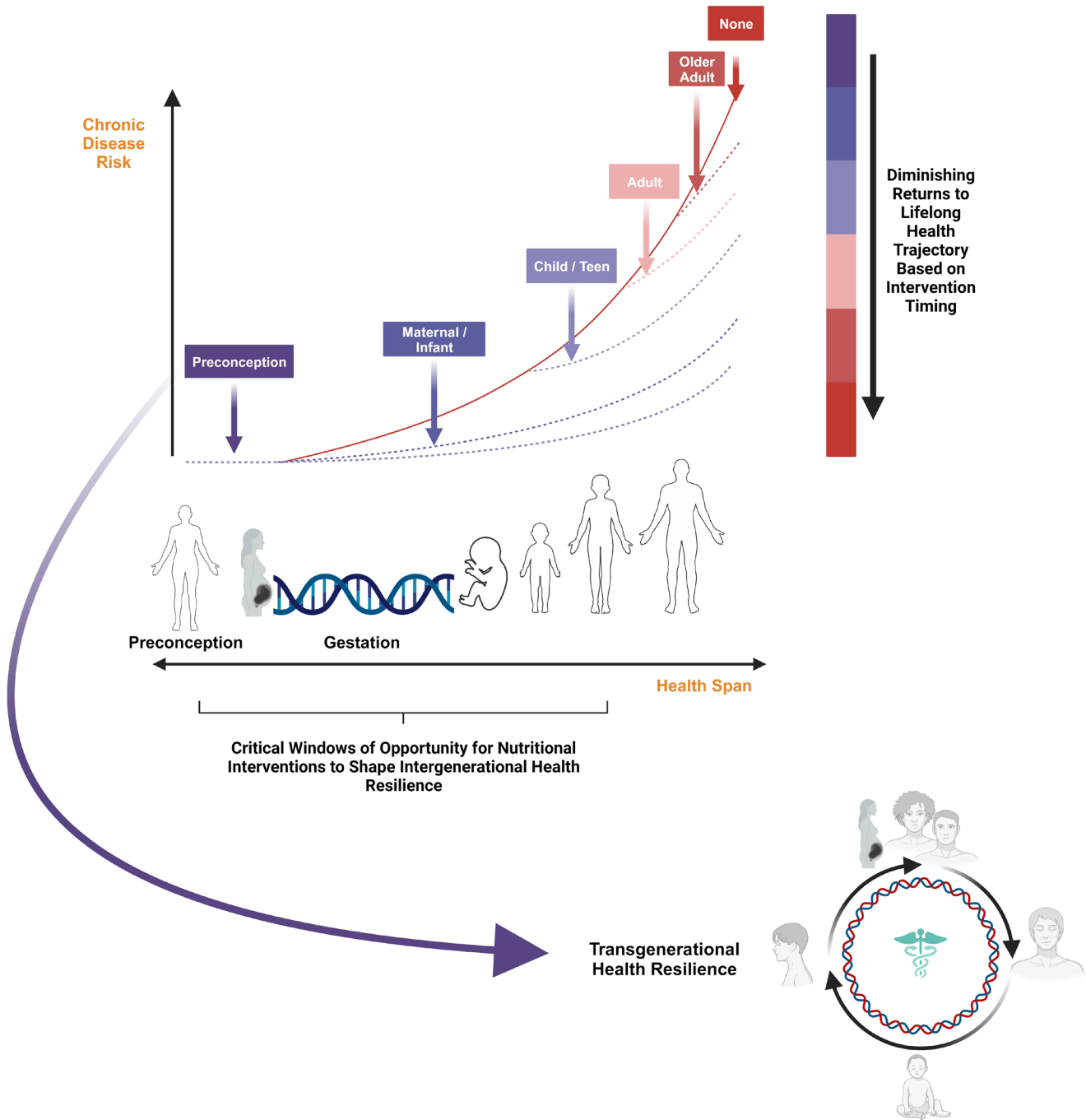


Figure 1.

Trajectories of phenotype and chronic disease risk throughout the health span with a particular focus on nutritional exposures and interventions. Individual risk trajectories are sensitive to interactions between biological factors and environmental exposures. The effectiveness of nutritional interventions is related to intervention timing and nutritional provision is particularly crucial during periconceptual time periods. Thus, intentionally personalized and life-stage oriented nutritional support can shift transgenerational health trajectories. (Adapted from Hanson and Gluckman, 2014)¹⁴ Therefore, maternal nutrition status during preconception, pregnancy, and postnatal periods is one of the most significant exposures with the profound potential to bolster maternal and child health outcomes spanning various domains.² Such outcomes, which have been linked to perinatal nutrition include but are not limited to maternal fertility, future chronic disease risk, lactation performance, perinatal complications, delivery outcomes, and maternal mental health as well as offspring birth outcomes, neurocognitive development, mental health, allergy and asthma risk, epigenetic modifications, and development of chronic diseases throughout the lifetime.^{1,6} Thus, policy interventions such as folic acid fortification in the United States (US) food system and current nutritional recommendations for perinatal periods have attenuated the

prevalence of nutrient deficiency-related complications, particularly in high-income countries.^{15,16} While this work has led to striking improvements in public health, we must align the aims of perinatal nutrition research, clinical practice, and policy to enhance health outcomes as there is a sizable interval between the appearance of deficiency symptoms and the full potential of optimized nutrition for health. It is time for a strong stance in support of the continuum of women's health to align with the provision of optimal nutrition throughout the lifespan to enter critical windows of influence on lifelong health outcomes well-nourished and in control. This approach has the power to transform health and resilience outcomes for generations (Figure 1).

It is essential to reiterate, that while it is understood that nutrient needs increase during pregnancy and lactation, there is a lack of population-specific evidence to support the current recommendations for perinatal nutrient reference intakes.⁴ Largely, Dietary Reference Intakes (e.g. RDAs) were established between 1997 and 2005, and only vitamin D and calcium recommendations have been updated subsequently.¹⁷ Additionally, while the regular consumption of multivitamin and mineral supplements is ubiquitously recommended for pregnant and lactating women before conception and during pregnancy and lactation, there are no standardized or harmonized recommendations among researchers, clinicians, and public health agencies regarding nutrient profiles, dosages, or nutrient forms.¹⁸⁻²⁰ Though it is recognized that the capacity of a multi-nutrient supplement to improve nutrition status is inherently related to all such factors. These inconsistencies contribute to the flawed foundation upon which the current landscape of perinatal nutrition stands and will be detailed in subsequent sections of this paper.

Critically, even in the landscape of suboptimal nutrition recommendations for pregnancy, there is emerging evidence to suggest that it is practically impossible for women to even meet such recommendations with diet alone.^{21,22} Global estimates suggest that 2/3 of women of childbearing age experience micronutrient deficiencies.²³ Furthermore, recent studies suggest that even in high-income countries, such as the US, micronutrient inadequacies are common.^{22,24} Unfortunately, assessment and reporting of usual dietary intake in representative samples of pregnant and lactating women tends to be limited.²⁵ However, 2013 systematic review and meta-analysis of dietary intake during pregnancy in high-income countries found that pregnant women have inadequate intakes of several crucial nutrients including folate and vitamin D.²⁵ These results were supported by a recent analysis completed of 1003 pregnant women in the US using data from the 2001-2014 National Health and Nutrition Examination Survey (NHANES) to assess nutrient intakes and the alignment of contemporary intakes with current dietary reference intake recommendations.²² Strikingly, the study findings suggest that with diet alone, 95% of women would fail to meet dietary recommendations for at least one nutrient. Moreover, of the 70% of pregnant women reporting the use of dietary supplements in this study, a significant proportion of pregnant women still failed to attain recommended intakes for critical micronutrients including folic acid, choline, vitamins D, C, A, K, and E, iron, calcium, potassium, and magnesium.²² The findings suggest that even with supplements, 1 in 3 pregnant women (aged 20-40 years) were at risk of shortfalls in vitamin D, magnesium, and vitamin E intake, with 1 in 10 at risk for inadequate intake of vitamin A, vitamin C, and vitamin B6 and minerals such as zinc.²² It is also important to note that supplement use was associated with the risk of iron and folic acid intakes above the current upper limit recommendations.

Thus, updated and enhanced nutritional supplement strategies are required, but not exclusively associated with a "more is better" approach. This study's findings illustrate the impact, though not the multifactorial etiological nature, of culminating factors in the modern world which predispose individuals, particularly vulnerable groups such as pregnant and lactating women, to nutrient inadequacies.²⁶ It further highlights the understanding that, as with food, all prenatal supplements are not created equal. This points to a need for optimized dietary supplementation with respect to appropriate dosing, bioavailable nutrient forms, and distinct personalization for perinatal specific health outcomes. These findings are even more poignant, as there is contemporary data to suggest that 97% of women report taking a prenatal supplement during pregnancy.²⁷ Moreover, additional findings from the work of Needed collaborators, including Emily Rydbom CN, HN, CNP, suggest that beyond assessment of dietary intakes, biomarker assessments in pregnant women signal a deficiency prevalence of up to 100% in nutrients such as vitamin D, which are critical to maternal and fetal nutrient status and health trajectories.²⁸ All of this should be interpreted with the understanding that dietary reference intakes are established for healthy individuals, and those with existing inadequacies or altered needs will likely require even higher amounts of nutrients or modified nutrient forms.²¹ Additionally, with evidence to suggest the current perinatal dietary recommendations are substandard, prevalence of deficiency and thus need for personalized supplementation is likely much higher than currently appreciated.

It is evident that even in developed countries, nutrient intakes and diet quality are suboptimal.^{22,25,26} However, this is driven and compounded by interactions among several factors which warrant dietary supplementation in perinatal periods to meet the vital nutrient needs which support both the mother and child during this critical window for shaping lifelong health outcomes.²⁶ The prevalence of western dietary patterns contributes significantly to consumption of highly processed, nutrient-poor, calorie dense options, which tend to be high in added sugar and sodium but poor in micronutrients such as iron, iodine, folate, vitamin B-12, vitamin D, choline, and omega-3 fatty acids.^{24,29,30} Additionally, food processing is associated with removal of nutrients, such as the loss of magnesium content through carbohydrate refinement processes.³¹ Moreover, much of the sodium consumed in the US is derived from processed food products which are largely not iodized, and most kosher and sea salts added in the home do not contain iodine.^{32,33} Therefore, with this evidence and the understanding that the western diet tends to be low in iodine-containing foods, it is unsurprising that pregnant women in the US have urinary iodine concentrations which do not meet World Health Organization (WHO) recommendations for iodine sufficient status.³⁴

Dietary patterns, such as vegan, vegetarian, and gluten-free diets are also associated with risks of nutrient deficiencies. For example, it is estimated that the prevalence of vegetarianism is 6% in US pregnant women and growing in popularity.³⁵ Nutrients such as vitamin B12 are concentrated in animal sources, so those following diets that restrict animal products have increased risk of vitamin B12 inadequacy.^{36,37} Additionally, the richest sources of choline, a vital nutrient for neurodevelopment, include animal-based products such as meat, dairy, and eggs.³⁸ It is important to highlight that 92% of pregnant women in the US have an intake that is below the adequate intake recommendation for choline, and the majority of dietary prenatal supplements available do not contain choline or adequate amounts of choline.^{22,38} There is also mounting evidence to suggest that an increasing proportion of individuals are following gluten-free diets, including those without celiac disease or gluten sensitivity.³⁹ Dietary patterns which replace gluten containing sources with gluten-free foods may increase the risk for low fiber intake as well as vitamin and mineral deficiencies including B vitamins, calcium, iron, zinc, and magnesium.^{39,40} Such shortfalls in nutrient intakes have been demonstrated in individuals with celiac disease adhering to gluten-free diets.⁴¹ It is important to consider that dietary patterns are adopted for various reasons, spanning medical, cultural, preferential, and environmental considerations, among others.⁴² Further, dietary patterns such as plant-based, vegetarian, and vegan diets are associated with significant health benefits through such shifts as augmented consumption of phytochemicals and fiber.^{43,44} However, those adhering to such dietary patterns require careful assessment and intentional supplementation based on intake patterns and nutritional status.⁴²

Moreover, the use of certain medications can impact nutrient absorption or metabolism, and thereby nutritional status, regardless of dietary pattern. For example, the use of oral contraceptives has been shown to modify the absorption of B vitamins, specifically vitamin B6.⁴⁵ This is a concern, given reports suggest that nearly 15% of women in the US ages 15-49 years utilize oral contraceptives, with higher prevalence of reported use (21.6%) in women ages 20-29.⁴⁶ Additionally, reports have suggested that 21.1% of women become pregnant one cycle after ceasing oral contraceptives.⁴⁷ Further, other prescribed medications such as proton pump inhibitors have the potential to interfere with both vitamin B12 and magnesium absorption and may affect the status of both nutrients.⁴⁸ Such findings are particularly concerning, given the rate of medication use during pregnancy is rising.⁴⁹

Food systems are complex in nature and influenced by both the environment and human activity, while in turn impacting the environment and human health.⁵⁰ Cultivation practice shifts have been associated with alterations in the nutrient density of food products, resulting in potentially lower mineral content.^{51,52} For example, monoculture farming practices diminish the availability of certain nutrients in the soil and promote soil degradation as nutrient depletion mounts.⁵³ Further, there exists intricate interplay between food systems, the environment, and nutrition, within the scope of human health. Climate change has resulted in insults to the sustainability of food systems, such as the diminished nutritional quality in certain crops due to increasing carbon dioxide production.⁵⁴ Cyclically, food systems and agricultural practice contribute to environmental erosion.⁵⁰ Studies which have aimed to assess the impact of crop growth conditions under varied carbon dioxide concentrations have found that carbon content is increasing at the expense of key nutrients including iron and zinc.⁵⁴

Furthermore, human exposure to environmental toxicants, such as non-essential trace elements is continuously increasing. It is estimated that more than 85% of US women of childbearing age have measurable levels of circulating mercury, lead, cadmium, and arsenic.⁵⁵ In the body, the absorption and retention of such toxicants may be sustained by

leveraging an individual's nutrition status, in turn potentially competing with essential nutrient absorption.⁵⁶ Thus, there is the potential for nutrient inadequacies to be exploited by environmental exposures, and such complex interactions may influence health outcomes particularly in pregnant and lactating women whose exposures inherently impact a developing baby. Poor dietary patterns and environmental exposures are also main contributors to the rise in obesity prevalence in the US, which is predicted to reach 50% by 2030.^{57,58} Evidence suggests that women with obesity have reduced micronutrient concentrations, in comparison to women with normal weight, and are more likely to present with deficiencies during gestational periods.⁵⁹ Moreover, endocrine disrupting chemicals, such as phthalates, interfere with hormone signaling thereby disturbing metabolism and contributing to the development of obesity and obesity related conditions.⁶⁰ Such shifts in metabolic processes inherently impact nutritional requirements and status and may have transgenerational impacts. Importantly, nutrient provision and improvements in nutritional status, through food or dietary supplements, may conversely reduce the effects of exposure to toxicants and exert a protective effect.

The aforementioned obesogenic environment has also been associated, as both a cause and consequence, with alterations to the gut microbiome; noting the gastrointestinal tract is a first line exposure to both nutrients and ingested toxicants.^{61,62} Such obesogenic exposures disrupt the integrity of intestinal barriers and unfavorably shift the composition of gut microbes.⁶² This dysbiosis has been causally linked to the development of chronic inflammatory conditions, via increases in gut permeability and chronic systemic exposure to bacterial lipopolysaccharide derived from gram negative bacteria.⁶³ The gut microbiome is also now recognized as key to host nutritional status through utilization and storage of consumed dietary compounds and provision of nutrients, such as short-chain fatty acids through fermentation processes. Relatedly, unfavorable alterations to microbial diversity and populations are linked to maladaptive modifications to nutrient metabolism.⁶⁴ The consequences of dysbiosis in pregnant and lactating women are not isolated to the mother. The fetal gut is primed during pregnancy by the maternal gut microbiome and there may be transfer of dysbiosis through pregnancy, delivery, and lactation.⁶⁵ The fetus may also be exposed to microbial products through modifications to intestinal barrier function. Further, it has been suggested that 72% of intestinal bacteria in infants delivered vaginally is received from the maternal microbiota, suggesting the role that mode of delivery plays in bacterial exposure and infant gut microbial colonization.⁶⁶ It is important to again note that obesogenic exposures may be attenuated by specific nutrients. Indeed, bioactive plant compounds such as polyphenols have anti-inflammatory and antioxidant properties and may be useful in mitigating inflammatory obesogenic exposures.⁶⁷

Finally, the landscape of environmental and lifestyle factors which contribute to the complex etiology of nutritional deficiencies experienced in pregnant and lactating women is further compounded by interactions with genetic factors which may modulate nutrient status. Several genetic factors have been discovered which impact nutrient utilization. One such factor is a known genetic polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene which can significantly modify folate metabolism.⁶⁸ This is significant, given the crucial role of folate in neural tube development. While increases in folate intake may offset risks of neural tube defects (NTDs), persistent modifications in folic acid metabolism could result in elevations in unmetabolized folic acid, which may lead to adverse health consequences.⁶⁹ There have also been single nucleotide polymorphisms (SNPs) associated with beta-carotene absorption and conversion to active vitamin A, which is notably different among individuals.⁷⁰ Therefore, as beta-carotene is the most common provitamin A carotenoid consumed from the diet and dietary supplements, such diversity in utilization inherently impacts the utility of beta-carotene alone to enhance vitamin A status. These serve as two important examples of genetic factors which modulate nutrient status beyond intake. Several genetic factors have been identified which impact other nutrients, such as those which result in alterations in choline utilization and homocysteine metabolism.⁷¹ It is therefore evident that a potent opportunity exists to harness the evidence regarding genetic variants which impact nutritional status and subsequent biological outcomes, to optimize nutritional strategies which can maximize benefits across a wide range of individual factors. The power of a dietary supplement approach in this context is the ability to leverage this information to formulate a product which overcomes multiple individual factors through careful choice of nutrient forms, doses, and mixtures, while causing no harm to the aggregate consumer population.

Taken together, the burden of undernutrition in high income countries is complex, multifaceted, and has a particular impact on vulnerable populations such as women in the perinatal period. It is also clear that dietary supplements are a crucial strategy to fill this nutritional gap, though dietary supplements available offer disparate nutrient profiles and organizational guidance has not reached consensus on the optimized strategy.¹⁹ This has generated widespread confusion as mothers and practitioners aim to navigate the choice of dietary supplements during this critical time frame. The culmination of

factors which contribute to the substandard nutritional status observed in women of reproductive age worldwide demands a nutritional supplement strategy which has harnessed the evidence to create the optimal formulation such that it aims to meet needs of diverse women and fortifies the bridge between research and practice for all mothers.

Perinatal periods are pivotal timeframes in which biological systems are particularly sensitive to environmental exposures which can shape development and risk for non-communicable conditions across the lifespan. There is unequivocal evidence that nutrition is a key modifiable factor which can condition lifelong outcomes for maternal and child health. The expectation of meeting increased nutrient demands during pregnancy through diet alone is realistically impossible for the majority of women. Though the burden of perinatal nutrient inadequacy is complex in nature, it is clear that intentional and personalized support with evidence-centered dietary supplements is a crucial strategy to fill nutritional gaps.

Need for high-quality evidence to substantiate or modify perinatal dietary reference intakes

Despite the evident demand to enhance our understanding of nutritional requirements for women during the perinatal period, adequate inclusion of women in biomedical research is historically lacking.⁷² The rhetoric would posit that exclusion of pregnant women from clinical research is done with the intention of protecting both the mother and fetus, while mitigating logistical complexities regarding recruitment and trial design. It has only been 30 years since the US Food & Drug Administration (FDA) reversed a guideline set in 1977 that recommended women of childbearing potential were inappropriate participants for early clinical trials, such that they be routinely excluded from clinical trials under the guise of fetal protection.⁷³ This recommendation had a pervasive impact on the design of clinical research and restricted access for women to a broad array of clinical trials, regardless of the policy's focus on early phase trials.⁷⁴ There has been mounting support for the equitable inclusion of pregnant and lactating women in research, though the wheels of change have not kept up with the health disparities experienced by vulnerable groups who have suffered from a lack of population-specific research.^{4,75} The exclusion of women from research^{4,75} which informed current nutrient reference values is another crucial example of such inequity and the focus of the following section.

The perfect storm for observed perinatal inadequacies in nutrition status is a culmination of the historical exclusion of pregnant and lactating women from high-quality studies utilized to inform the perinatal dietary reference intakes combined with the issue that reference intakes were established with the goal of preventing nutrient deficiency rather than maximizing population-specific health outcomes.⁴ A comprehensive assessment of perinatal nutrient requirements demands the evaluation of intricate biological and environmental factors. Within the complex landscape of perinatal physiology, pregnancy is associated with shifts in metabolism and nutrient absorption, expansion of plasma volume, and alterations in urinary excretion.¹ The perinatal period is one characterized by upregulated needs for most nutrients, and the requirements for this vulnerable group have not been established with research derived from this population and have largely ignored maternal and fetal health outcomes as indicators in setting nutrient reference values.⁴

Nutrient reference values, termed dietary reference intakes in the US and Canada, are established based on the evidential support for individual nutrients and include the estimated average requirement (EAR), the adequate intake (AI), the recommended dietary allowance (RDA), and the tolerable upper intake level (UL).³ The RDAs are set to reflect nutrient intakes which ostensibly meet the needs for 97-98% of healthy people and are derived from the EAR. The AI is set based on estimated nutritional intakes in healthy individuals, and in place of an RDA when adequate evidence to support an EAR is lacking.³ Agencies which establish nutrient reference values utilize animal research, nutrient balance studies, controlled feeding studies, biochemical indicators of tissue accretion and function, indicators of health outcomes, and epidemiological evidence as the basis for recommendations. It is also imperative to reiterate that efforts to establish nutrient reference values were aimed to mitigate deficiencies in the population whereas upper limit values were set for healthy individuals with adequate micronutrient status.⁷⁶ These approaches are limited, such that reference values do not currently address the expansive gap between nutritional deficiencies and optimal provision of nutrients to support full health.⁷⁶ Moreover, when inadequacies or deficiencies are present, such as have been demonstrated previously in pregnant women, intakes exceeding the UL may be necessary to remedy such deficits.²¹ Therefore, shortfalls exist in our current understanding of what constitutes optimal nutritional nourishment at the population level, with vulnerable subgroups being particularly susceptible.

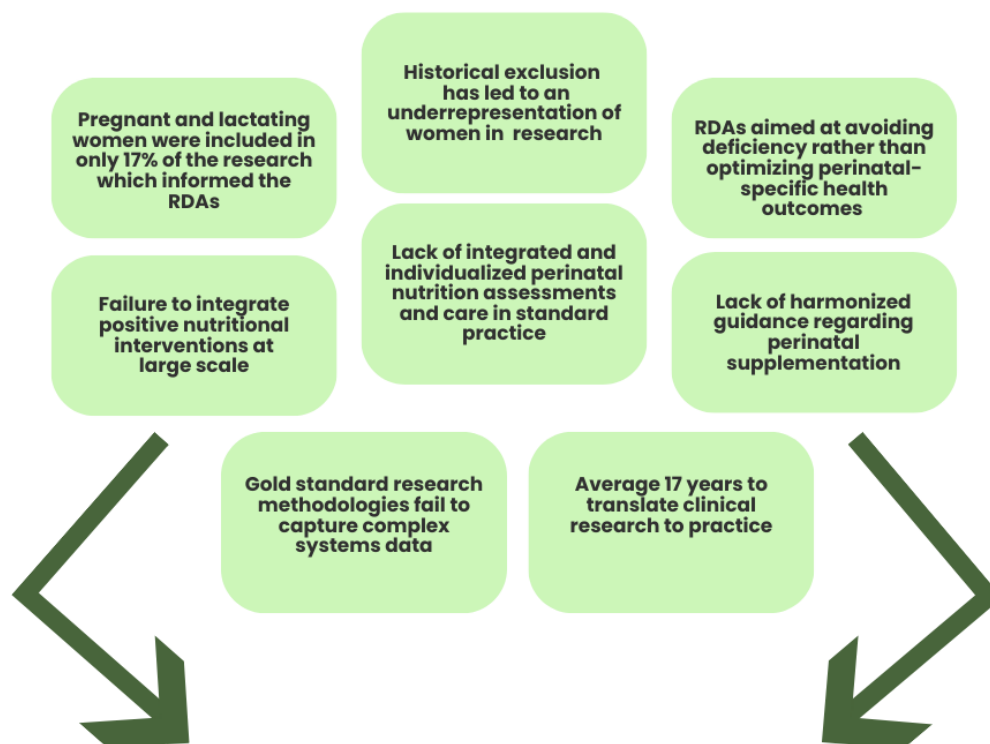
There is substantial literature to suggest that perinatal exposures are drivers of lifelong health outcomes for the mother and offspring, with nutrition being one of the most critical exposures during this highly sensitive period.⁹ Given such

compelling evidence, it would stand to reason that there is an essential need to include pregnant and lactating women in nutrition research which informs nutrient recommendations for these phases of life. However, a recent analysis aimed at assessing the quality of evidence utilized to inform the micronutrient reference values for pregnancy found that pregnant and lactating women were included in only 17% of studies which also grossly lacked reporting of racial and ethnic diversity of the study samples.⁴ Furthermore, among the studies which used high quality methods to inform nutrient reference values, only 17.5% included pregnant or lactating women. It was also noted that most reference intakes for pregnancy were established based on reference intakes for nonpregnant women, some of which were determined based on data from males.⁴ Thus, dietary reference intakes for pregnant and lactating women were largely derived from modeling methods, most often the factorial approach which estimates nutrient requirements to replace losses and the additional amounts needed to support pregnancy or lactation. A prime example is the AI for choline, which was adjusted for nonpregnant women using data from research aimed to prevent liver damage in men.⁷⁷ The AI for pregnancy of 450 mg/day was derived from the factorial method considering the fetal and placental accretion of choline.^{4,77} However, there is accumulating research to suggest that the current AI for choline in pregnancy is in fact not adequate. It has been found that pregnant women consuming 480 mg/day of choline present with circulating concentrations of choline metabolites which are 40-60% below levels in nonpregnant women consuming equivalent choline.⁷⁸ This is only one crucial example among several nutrients. However, considering reports that only 8% of pregnant individuals currently meet this substandard threshold for choline intake, the example serves to illustrate the urgent demand to address these research gaps to enhance the perinatal specificity of nutritional recommendations.²²

Further, health-related outcomes specific to pregnancy and lactation were not selected as indicators for setting reference intakes.^{4,79} For example, the functional indicator utilized to determine adequate folate intake used to set the RDA for women, regardless of pregnancy or lactation status, was erythrocyte folate rather than a reduction in NTD risk.⁷⁷ Moreover, indicators of nutritional status were selected based on studies in which over 99% of the population consisted of nonpregnant women and men.⁴ This is a fundamental issue, as physiologic shifts in pregnancy, such as alterations in plasma volume, may impair the utility of biochemical indicators considered sufficient in nonpregnant individuals. Finally, certain nutrients may confer adverse health risks when consumed in excess, particularly for vulnerable population subgroups such as pregnant women in which excesses may result in teratogenesis.²¹ However, for the majority of micronutrients for which nutrient reference values exist, no studies which informed the ULs included pregnant or lactating women.⁴

It is time for not only a shift in this narrative, but a call to action (Figure 2). The ethical and functional protection of pregnant and lactating women is maximized through intentional design of, and inclusion in, high quality research – not exclusion. Recent evidence suggests that pregnant women are not optimally nourished, even by current standards of recommended intakes.²² There exists a pressing need to comprehensively assess baseline nutritional status using harmonized and validated biomarkers, to contribute to the body of evidence which informs pregnancy specific reference ranges. There is a necessity to reevaluate the current dietary guidance for pregnancy and lactation with respect to pregnancy specific outcomes and the application of rigorous research methods in pregnant and lactating individuals.⁴ Indeed, in recent years there have been strides in research which aims to optimize our understanding of broad perinatal nutrition needs. Much of these findings demonstrate that the current RDAs for perinatal periods are substandard, though a sustained focus on this research is necessary to understand optimized needs and practical translation of research to practice.⁵ Unfortunately, even with novel research findings emerging to support shifts in the current perinatal nutritional model, the average time frame for translation of clinical research to clinical practice is strikingly 17 years.⁸⁰ Women and children cannot be left to suffer in limbo as high-quality evidence emerges in support of emphasizing shifts in nutritional needs and a focus on personalized nutritional care in perinatal windows.^{28,81} This is clear, as even under current recommendations many women do not have access or receive nutritional counseling during pregnancy.⁸² It is also necessary to recognize that nutritional model shortfalls in the perinatal period are superimposed on the lack of standard, and thus access to, preconception maternal and paternal nutritional care in routine practice. Moreover, we must consider the evidence that nearly half of pregnancies are unplanned, further predisposing individuals with poor nutrition to critical inadequacies in early gestation.⁸³ Thus the overall approach to shift periconceptional nutrition standards must consider and prioritize parental health as a continuum.

Historically, pregnant and lactating women have been excluded from biomedical research, leading to a lack of understanding of their specific nutritional needs. The current dietary reference intakes, such as RDAs, for these periods are largely based on evidence from non-pregnant individuals. It is crucial to include women in high-quality research to tailor nutritional recommendations to optimize perinatal health outcomes and address health disparities.



A Broken Perinatal Nutritional Paradigm, with 95% of Pregnant Women at Risk for Nutrient Inadequacies.

Figure 2.

Key contributing factors leading to the current substandard perinatal nutritional paradigm. It should be noted that all such factors are superimposed on the intricate interactions among biological and environmental exposures which influence nutritional status. It is time to capitalize on contemporary evidence and prioritize further research in efforts to spur action and create change in the approach to perinatal nutrition.

Need for harmonization of recent evidence to support shifts in perinatal nutrient recommendations with a particular focus on perinatal nutritional supplements.

The state of the evidence suggests that current dietary guidance for pregnant and lactating women is lacking, yet women are struggling to attain such thresholds of nutrient intake even with additional supplementation.^{4,22} While the factors which drive the need for additional dietary supplementation have been outlined previously in this paper, it is important to emphasize that the expectation of meeting increased nutrient demands during pregnancy through diet alone is realistically impossible for the majority of women. Moreover, a substantial body of evidence is available to corroborate that supplementation of several nutrients in quantities or forms which differ from the current guidance confer positive outcomes for maternal and child health.^{5,78,84} The lack of harmonized recommendations regarding perinatal supplements flies in the face of the literature which suggests that current dietary recommendations are substandard and evidence which has examined the effects of nutrient provision with respect to maternal and child health indicators. Moreover, the lack of attention to the suboptimal nutrition status of women of reproductive age disarms women and

clinicians of guidance in their approach to perinatal nutrition.

Beyond the need to revisit and critically assess nutritional requirements in pregnancy, attention must also be paid to the current market of prenatal supplements and supplemental nutrient forms with an emphasis on the present evidence base for optimized guidance. Several available prenatal supplements utilize broad spectrum single-pill strategies with cost effective nutrient matrices which may differ from nutrient forms supported by research and have limited efficacy and bioavailability.^{19,85} The bioavailability of supplements is impacted by compositional elements, quantities of ingested nutrients, the presence of other compounds both active and inactive, and homeostatic mechanisms.⁸⁶ All of these factors, among others, must be carefully considered to generate an optimal nutritional supplement approach. Prenatal supplements may also include fillers and additives which can lead to harmful exposures and inadequate nutrient provision during the highly nutrient-sensitive perinatal period.⁸⁷ Strikingly, a recent study investigating contaminant exposure from 26 prenatal multivitamin and mineral supplements reported that nearly half of supplements exceeded toxicity standards for lead, with other heavy metals such as aluminum and titanium present in the samples.⁸⁷ Moreover, analyses of widely utilized prenatal supplements suggest that the nutrient quantities expressed on labels differ from the quantity truly contained in the supplement.⁸⁸ It has also been suggested that even prescription prenatal supplements do not adequately replenish nutritional gaps for several nutrients due to the strong institutional focus on folic acid and iron provision.⁸⁹ Therefore, it is not shocking that substandard recommendations for perinatal supplementation have resulted in widespread nutrient inadequacies experienced by the vulnerable population subgroups of pregnant and lactating women.

It is time to take the reins and leverage the literature which has grown substantially in support of supplemental nutrient provision spanning from preconception through postpartum periods. Pregnancy represents a critical window of opportunity to intervene and improve nutrient status; thereby augmenting intergenerational health trajectories. Needed has examined the evidence, and harnessed additional perspectives from practitioners, to cultivate a holistic dietary supplement strategy which aims to fill critical nutrient gaps essential for augmenting perinatal health and lifelong health outcomes. The following sections will provide pivotal insights into the evidence utilized to develop and support the Needed approach.

There is growing evidence to support that current dietary recommendations for perinatal periods are substandard, with women and children paying the price. This is compounded by a lack of harmonized recommendations for perinatal supplements, and a market of prenatal supplements which varies in terms of nutrient profiles, nutrient forms, efficacy, and safety. However, supplementation with various nutrients, often in variable forms or doses differing from the current recommendations, has been shown to confer positive outcomes for maternal and child health and requires attention for implementation into current standards and further exploration.

Evidence to support the Needed approach

Macronutrients – Protein

Protein intake during pregnancy is vital for maternal protein deposition and the support of fetal growth and development. While most of the fetal protein weight gain occurs later in gestation and whole protein turnover increases in the second and third trimesters, maternal modifications to protein metabolism begin ahead of increases in fetal requirements.^{90,91} These data support elevated needs for dietary protein throughout pregnancy, though greater intake in later gestation may be indicated. The current reference intakes recommend an RDA of 1.1 g/kg/day of dietary protein during pregnancy.⁹¹ However, this guidance is derived from factorial adjustments of nitrogen balance data from studies in nonpregnant individuals with estimated additions for protein maintenance, as well as tissue accumulation and growth.⁹² There is specific evidence that the current dietary reference intakes for protein intake during pregnancy are inadequate. Nitrogen balance methods, apart from the impracticality of use in pregnant and lactating women, are no longer considered the gold standard for evaluating protein requirements.⁹³

However, the use of stable isotopes is safe and essential for examining nutrients in pregnant and lactating populations.⁹³ A more recent method termed indicator amino acid oxidation (IAAO) was developed which employs stable isotopes to determine the utilization of labeled amino acids in response to varying protein intakes, which allows for the non-invasive direct assessment of protein requirements. The IAAO method has been harnessed to assess protein needs in pregnancy,

and the EAR derived from pregnant women was reported to be 1.2 g/kg/day between 11-20 weeks of pregnancy and 1.52 g/kg/day during late pregnancy.⁵ These data derived from rigorous research methods in healthy pregnant women unsurprisingly differ from the current RDAs, which underestimate needs by 15-27%.⁵ Additionally, the current dietary reference intakes for protein are static and this emerging population-specific data enhances the understanding of pregnancy stage-related estimates.

These findings are reflected in evidence from clinical trials with aims to supplement women with high-quality protein during the perinatal period. An early study in this field found that increasing protein intake to an average of 101 g/day in pregnant women with low-income status was associated with benefits in birth outcomes.⁹⁴ Moreover, IAAO studies conducted in lactating women suggest that protein demand is also substantially higher than the current guidance for protein intake during lactation, about 61-81% above the EAR.⁹⁵ Though assessment and reporting of protein intakes among pregnant women is limited, there is evidence to suggest that 1 in 8 pregnant women have inadequate protein intakes.⁹⁶ Dietary protein supplements represent a key strategy which can be employed to supply high-quality protein to women with suboptimal protein intakes from diet alone to support perinatal health.

Further, it has been demonstrated that the needs for both indispensable and dispensable amino acids increase during pregnancy.⁹⁷ For example, a recent study examined glycine demand during mid and late pregnancy using IAAO methods. The researchers concluded that glycine demands increase in late pregnancy and should likely be considered conditionally indispensable during this window of gestation.⁹⁷ Glycine constitutes about 33% of the amino acids in the most abundant protein in humans, collagen.⁹⁷ Additional studies have also suggested de novo glycine synthesis does not meet biological demands, particularly during pregnancy.^{98,99} This is critical, as glycine contributes to one-carbon metabolism and impaired status may impact maternal and fetal methylation and thereby cellular function.¹⁰⁰ Importantly, studies have demonstrated that dietary collagen intake can improve health outcomes.¹⁰¹ While collagen is considered an incomplete protein source, due to the absence of the indispensable amino acid tryptophan, a recent study demonstrated that substitution of daily dietary protein with collagen in levels up to 36% would still allow indispensable amino acid requirements to be achieved.¹⁰² Additionally, of particular note during perinatal periods collagen contains dispensable amino acids such as glycine, which likely provide additional benefits.

Emerging evidence from studies using IAAO methods suggests that the protein requirements for pregnancy and lactation are higher than current recommended intakes. These findings emphasize the importance of considering trimester-focused estimates and providing high-quality protein supplements for pregnant women with suboptimal protein intakes. Additionally, amino acids like glycine, which play a crucial role in one-carbon metabolism and cellular function, may be conditionally indispensable during pregnancy, and dietary collagen intake can offer benefits for maternal and fetal health.

Macronutrients – Omega-3 Fatty Acids

Several studies have suggested that greater consumption of omega-3 polyunsaturated fatty acids (PUFAs) is associated with improved perinatal outcomes. Specifically, fetal docosahexaenoic acid (DHA) concentrations increase in later stages of pregnancy and such accretion is vital for fetal growth, brain structure and development, and numerous neuronal functions.¹⁰³ DHA is also integral to the development of the placenta.¹⁰³ High levels of DHA accumulate in the cell membranes of retina and brain and DHA constitutes 15% of all fatty acids in the prefrontal cortex.^{104–106} While the long chain omega-3 PUFAs DHA and eicosapentaenoic acid (EPA), present in fish, krill, and algae, can be converted from alpha-linolenic acid (ALA) found in plant-based dietary sources, limited conversion necessitates the consumption of DHA and EPA directly from food sources or dietary supplements.¹⁰⁷ Thus, the Dietary Guidelines for Americans and the American College of Obstetricians and Gynecologists (ACOG) recommend that pregnant or breastfeeding women eat 2 to 3 servings per week of fish with low mercury content.^{108,109} Additionally, other organizations have suggested women consume 200–400 mg/day omega-3 fatty acids.^{110–112} However, it is apparent that women do not achieve such intake levels of DHA and EPA, and both women of childbearing age and pregnant women consume significantly less fish than is recommended.¹¹⁰

A recent Cochrane systematic review evaluated the effects of prenatal long chain omega-3 PUFAs, from both supplements and dietary intake, on maternal and child health outcomes. This study included data from 70 randomized controlled trials including nearly 20,000 women.¹¹³ The analyses concluded that preterm birth < 37 weeks and early preterm

birth < 34 weeks were lowered in pregnant women receiving omega-3s.¹¹³ The findings also suggest that omega-3 intake may reduce risk of perinatal death and low birth weight infants.¹¹³ Moreover, recent studies have found that low circulating concentrations of long chain omega-3s have been associated with preterm birth and prenatal depression.^{114,115} Such analyses support the need for additional DHA and EPA to bolster maternal and fetal health outcomes and highlight the importance of correcting present widespread perinatal inadequacies in omega-3 intake. Recently, a randomized multi-site clinical trial compared a low dose of DHA (200 mg/day) to a high dose of DHA (1000 mg/day) and demonstrated that 1000 mg/day of DHA was superior for prevention of early preterm birth and preterm birth, with particular benefits realized in those with low DHA status at baseline.¹¹⁶ A secondary analysis of this study also noted that DHA may moderate risk for preterm birth through the immunomodulatory effects observed at higher doses of DHA intake.¹¹⁷

Additionally, evidence from cohort studies suggests that pregnancy-associated reductions in omega-3 PUFA status increase the risk for postpartum depression (PPD).^{118,119} While the etiology of PPD is complex and not yet fully elucidated, nutrient inadequacies and inflammation have been posited as having mechanistic involvement.¹²⁰ Importantly, modifications to nutrient provision, especially nutrients such as omega-3 fatty acids with known anti-inflammatory and pro-resolving activities, may present a viable strategy to attenuate risk.¹²¹ A recent review examining the effects of omega-3 PUFA supplementation on depression during pregnancy or PPD following childbirth found that supplementation with EPA during pregnancy may reduce symptoms of depression during pregnancy and postpartum.¹²⁰ Further a recent meta-analysis of randomized controlled trials concluded that omega-3 supplementation improved symptoms of depression in women compared to a placebo during pregnancy and postpartum.¹²²

Taken together, given that over 95% of women of reproductive age and pregnant women are not meeting DHA and EPA intakes which would be expected from 2-3 servings of fish per week (250 mg/day), there is strong evidential support for the use and safety of high dose omega-3 fatty acids.^{113,123} Moreover, it has been demonstrated that DHA levels are diminished by as much as 50% during pregnancy, and full recovery may not be realized until several weeks postpartum.¹²⁴ Thus, aligning with the Needed approach, omega-3 support should continue postpartum and beyond especially within the scope of multiple pregnancies.

Omega-3 polyunsaturated fatty acids, particularly DHA and EPA, play a critical role in perinatal health, affecting fetal growth, brain development, and placental function. Current guidance suggests that pregnant or breastfeeding women consume 2 to 3 servings of low-mercury fish per week or 200–400 mg/day of omega-3s to achieve optimal intake. However, most women do not meet these recommendations, and supplementation with higher doses of omega-3s has been shown to reduce the risk of preterm birth, perinatal depression, and low birth weight, underscoring the importance of addressing omega-3 inadequacies during pregnancy and beyond.

Macronutrients – Carbohydrates: A focus on dietary fiber

Carbohydrate needs are elevated in pregnancy, given glucose utilization by both maternal and fetal brains, as evidenced by the carbohydrate EAR for pregnancy of 135 g/day compared to 100 g/day for nonpregnant women.⁹² Additionally, the EAR of 160 g/day in lactation was established based on maternal glucose needs and the lactose content in human milk. However, it has been extensively demonstrated that quantity and quality of carbohydrates are not equal, and quality of carbohydrate has also been shown to impact maternal and fetal health as well as delivery outcomes.¹²⁵ Additionally, pregnant women in the US and Canada have been found to have the highest carbohydrate intakes from diet.¹²⁶ A recent analysis of NHANES data also suggested that nearly 15% of energy consumed by pregnant women was derived from added sugars.¹²⁷ Moreover, though adequate fiber intake has been linked to a wide range of health benefits including lower risk for certain cancers and coronary heart disease and improvements in glucose regulatory parameters, no pregnancy associated outcomes were utilized to establish the AI for fiber in pregnancy.^{128–130} While current recommendations for fiber intake during pregnancy are set to an AI of 28 g/day, evidence suggests that pregnant women consume significantly less fiber than the current AI.¹²⁶

Additionally, the prevalence of obesity has been associated with poor dietary quality, including low dietary fiber intake.¹³¹ Moreover, maternal obesity has been linked to adverse health outcomes and increased risk for chronic disease and neurocognitive deficits in both the mother and offspring.¹³² Recent evidence suggests an important link between maternal obesity and lifelong chronic disease risk in the mother and offspring may be the adverse modulation of the gut microbiome.¹³³ Interestingly, dietary fiber provides a key substrate for fermentation and production of short-chain fatty

acids (SCFAs) by the gut microbiota which can be absorbed and utilized by the host.¹³⁴ Thus, dietary fiber intake has been evidenced to favorably modulate the intestinal flora.¹³⁵ SCFAs have a wide range of biological effects in humans, including effects on the host brain, inhibition of inflammatory pathways, and support for the immune system response.¹³⁶ SCFAs are emerging as a critical indicator of healthy intestinal milieu and may influence maternal health supporting normal glycemia and blood pressure.¹³⁷⁻¹³⁹ Additionally, a dysregulated gut microbiome has been associated with maternal and fetal adverse outcomes in pregnancy. For example, a lower abundance of SCFA producing bacteria has been noted in preeclamptic pregnancies.¹⁴⁰

Importantly, low fiber intake has been associated with an increased risk of combined adverse outcome (cesarean section, premature delivery, and/or small for gestational age [SGA]).¹²⁵ There is also evidence to support that dietary fiber supplements administered in pregnancy also may improve cardiometabolic parameters and delivery outcomes in pregnant women with GDM.¹⁴¹ Additional and compelling research has demonstrated that modulating dietary fiber intake during pregnancy has beneficial effects on the gut microbiome and the offspring's immune function, metabolism, and cognition.¹⁴²⁻¹⁴⁴ It is known that changes occur to the maternal microbiome and transmission of the intestinal flora from mother to offspring is imperative to offspring microbiome development, though this will be discussed in subsequent sections of this paper.¹⁴⁵ Thus, supporting a healthy microbiome through dietary fiber intake can modulate metabolic and immune programming in offspring and have powerful impacts on lifelong health outcomes. As such, fiber intake, diet quality, and supplemental support could facilitate both short and long-term health in mom and baby to prevent or help manage certain pregnancy-associated complications such as gestational diabetes (GDM), preeclampsia, or infections, and to prevent future complications such as asthma or allergies in children.^{135,146,147} Administration of pro- and prebiotics during pregnancy and lactation can also support the maternal microbiome and represent a safe option to optimize these periods of life and prevent adverse outcomes.¹⁴⁸

Many pregnant women fall short of recommended fiber intake, and low fiber intake has been associated with an increased risk of adverse pregnancy outcomes. Additionally, dietary fiber intake plays a role in modulating the gut microbiome, which can influence maternal and fetal health and may impact lifelong health outcomes for both the mother and child. Dietary fiber, pro- and prebiotics are potential safe strategies to support maternal microbiome and optimize health during pregnancy and lactation.

Micronutrients – One carbon metabolism

In the process of one-carbon metabolism, nutrients consumed from the diet or dietary supplements provide methyl groups needed for DNA methylation and epigenetic modification, thereby modulating gene expression.¹⁴⁹ Such nutrients which contribute to one-carbon metabolism as methyl donors or cofactors include folate, choline, vitamin B6, vitamin B12, and riboflavin.¹⁵⁰ As previously stated, the perinatal period is a particularly sensitive time frame for nutritional exposures, such that the fetal epigenome is being shaped as DNA methylation patterns are established.¹⁴⁹ The exposure or inadequate exposure to nutrients implicated in the one-carbon cycle, may enduringly modify offspring gene expression, through alterations in the availability or transfer of methyl groups to DNA.¹⁴⁹ Therefore, the provision of micronutrients involved in one-carbon metabolism are crucial to maternal and fetal health outcomes. Further, adverse pregnancy outcomes such as fetal growth disorders, congenital birth defects, and preterm delivery have been related to deficiencies in these nutrients.¹⁵¹⁻¹⁵³ However, the consumption pattern of one-carbon cycle nutrients has shifted, and many women do not consume adequate amounts from the diet during perinatal periods.²² Additionally, the intake of certain nutrients, such as synthetic folic acid from dietary supplements, may exceed recommendations and result in increased levels of unmetabolized folic acid.²² This is a particular concern for women who exhibit polymorphisms linked to altered folate utilization.

During the perinatal period, the maternal diet plays a significant role in shaping the fetal epigenome and gene expression. Nutrients like folate, choline, vitamin B6, vitamin B12, and riboflavin, which are involved in one-carbon metabolism, provide methyl groups essential for DNA methylation and epigenetic changes. Inadequate intake of these nutrients has been associated with adverse pregnancy outcomes, especially for women with altered one-carbon nutrient utilization due to genetic factors.

Folate

Folate is required for the pathways involved in one-carbon metabolism which supports methylation, DNA synthesis, and amino acid metabolism.^{154,155} However, the interactions of folate with other B vitamins in this network of pathways is essential to one-carbon metabolism. Therefore, even with adequate folate in the diet, deficiencies in vitamin B12, vitamin B6, and riboflavin or genetic polymorphisms can impede these processes.^{68,156,157} Therefore, it is important to consider both concentrations and forms of these micronutrients with respect to perinatal supplementation. To illustrate this point from a biological standpoint, in the one-carbon cycle tetrahydrofolate (THF) is converted to 5,10, methylene THF, which requires vitamin B6 as a cofactor.¹⁵⁷ Subsequently, it is either reduced to 5-methyltetrahydrofolate (5-methylTHF), a reaction catalyzed by the riboflavin-dependent enzyme MTHFR, or contributes to nucleic acid synthesis. 5-methyl THF is required by methionine synthase for the conversion of homocysteine to methionine, a reaction which requires vitamin B12. This conversion of homocysteine to methionine is essential as it leads to the generation of S-adenosylmethionine (SAM), the central methyl donor required for the control of vital physiological processes.^{158,159} This provides context to the interdependency of nutrients to support optimal function of biological processes and the need for a comprehensive, rather than single nutrient approach to support health outcomes in mothers and offspring.

Folic acid fortification is a prime, yet imperfect, example of the power of dietary supplementation to improve offspring outcomes. Folate plays a critical role in tissue growth and adequate intake is particularly important in the perinatal period.^{154,160} Given the role of one-carbon metabolism in neural tube development, this population health strategy reduced NTDs in the US alone by 35%.¹⁶¹ However, despite such compelling evidence to support folic acid supplementation for NTD risk reduction preconceptionally, the current RDAs for nonpregnant women as well as pregnant and lactating women, were established to maintain red blood cell (RBC) folate.⁷⁷ Thus, the reduction in NTD risk was not considered in the current recommendations. Therefore, the RDA, which ranges from 400 to 600 mcg DFE or 240–360 mcg folic acid for women, is markedly lower than recommendations set by the US Preventive Services Task Force (USPSTF) of 400–800 mcg supplemental folic acid/day.¹⁶² The primary functional indicator utilized by the USPSTF was the reduction in NTD risk, and recommendations are inclusive of women of reproductive age.¹⁶²

Importantly, folate plays an essential role in pregnancy maintenance, as folate supports nucleic acid and amino acid synthesis and normal cell division.¹⁶⁰ Notably, polymorphisms in genes such as MTHFR which regulate folate metabolism, as well as deficiencies in vitamin B12 can result in dysregulated homocysteine metabolism and increased risk of pregnancy loss.^{163,164} Further, several studies have demonstrated hyperhomocysteinemia as a risk factor for early pregnancy loss.¹⁶⁵

Moreover, all current nutrient reference values and recommendations for perinatal folate intake specify folic acid as the supplemental form. Importantly, neither folate or folic acid are active forms metabolically, and the reduction of folic acid is necessary to carry out its biological functions.¹⁶⁶ In the body, folic acid is converted to L-5-MethylTHF, or L-methylfolate, via a series of enzymatic reactions, though the final step requires MTHFR.^{167,168} However, as noted previously in this paper, some individuals present with a polymorphism in the gene encoding MTHFR and have reduced MTHFR activity with impairments in folic acid metabolism. It is estimated that 40-60% of the population have polymorphisms which impact folate conversion.¹⁶⁹ Considering this evidence, it is unsurprising that many studies have examined the use of the biologically active form of folate, L-methylfolate, as this bioavailable form ensures adequate amounts of folate are provided even in those with genetic variations which influence folate conversion.¹⁷⁰ A recent published opinion by the European Food Safety Authority (EFSA) also noted the enhanced bioavailability of L-methylfolate compared to folic acid, indicating a 2.0 DFE conversion factor for L-methylfolate compared to the 1.7 conversion factor for folic acid.¹⁶⁸ In a recent randomized placebo-controlled trial of 144 women of reproductive age, the authors found that supplementation with L-methylfolate increased RBC folate concentrations to a greater extent than folic acid.¹⁷¹ Further, L-methylfolate supplementation has conferred similar decreases in homocysteine as folic acid forms.¹⁷² This is particularly promising, given that excessive unmetabolized folic acid is associated with exacerbation of B12 deficiency and neurocognitive impairment.^{166,173} Studies have also supported that maternal excesses in folic acid may modify offspring DNA methylation and elevate cardiometabolic risks in offspring, further raising concerns about health risks of unmetabolized folic acid.^{174,175} Folic acid forms of supplementation may also increase unmetabolized folic acid in human milk, which is less bioavailable to the child.⁶⁹ In a study which compared supplementation with 600 mcg of folic acid or a biologically active folate form during pregnancy it was demonstrated that folic acid forms increased the mean amount of unmetabolized folic acid in human milk collected one-week postpartum, compared to active folate supplementation.⁶⁹

Folate is essential for one-carbon metabolism, impacting DNA methylation, DNA synthesis, and amino acid metabolism. However, this process depends not only on folate but also on the interactions with other one-carbon nutrients. While folic acid fortification has significantly reduced neural tube defects, the active form of folate, L-methylfolate, may be more effective for supplementation especially for individuals with genetic variations affecting folate conversion.

Vitamin B12

Folate alone is not sufficient to support maternal and child health in the above context as the efficiency of the one-carbon cycle depends on multiple nutrients.¹⁷⁶ Vitamin B12 has also been established as a key nutrient involved in one-carbon metabolism, nucleic acid synthesis and genomic stability, and DNA methylation.¹⁷⁷ Thus, vitamin B12 is critical to maternal health and a crucial regulator of fetal growth and development. Unsurprisingly, deficiencies in vitamin B12 have been associated with poor maternal and offspring outcomes.¹⁷⁸ Low vitamin B12 status during pregnancy is increasingly common, and is associated with intrauterine growth restriction, low birth weight, preterm birth, and NTDs.^{179–182} Strikingly, a study in Canada suggested that 34% of NTDs may be linked to suboptimal vitamin B12 status.¹⁸³ Low maternal vitamin B-12 status has also been associated with an increased adiposity and incidence of GDM in pregnancy, and incident diabetes in later maternal life.¹⁸⁴ Critically, maternal vitamin B12 status also has implications for vitamin B12 concentrations in the infant, which can adversely impact fetal development.^{185,186} These findings may be related to the involvement of vitamin B12 in DNA methylation patterns and altered B12 status leading to adverse modifications in gene expression.¹⁷⁶ It has been shown that fasting plasma homocysteine and low vitamin B12 concentrations during pregnancy are associated with metabolic disturbances in offspring.^{187,188} Moreover, there is a growing body of evidence to suggest that exposure to suboptimal vitamin B12 can impair neurocognitive development and outcomes in offspring.^{178,189} Interestingly, studies have reported that vitamin B12 intakes among pregnant women do not currently meet the current recommendations.²² This may point to dietary reference intakes which are below actual needs to support maternal and fetal health, as well as lifelong outcomes.

In contrast, circulating maternal vitamin B12 levels between 312 to 408 pg/mL in the first trimester have been associated with improved infant motor, language, and cognitive performance compared to lower levels of vitamin B12 (<312 pg/mL) at 40 days postpartum.¹⁸⁹ Importantly, a recent study demonstrated that supplementation with 250 mcg/day of vitamin B12 during pregnancy and lactation can significantly improve vitamin B12 status in mothers, infants, and human milk.¹⁹⁰ Additionally, this study found that maternal supplementation with vitamin B12 enhances vaccine responses in mothers and may potentially attenuate infant inflammatory responses.¹⁹⁰ Vitamin B12 supplementation during pregnancy has also been demonstrated to not only recover maternal B12 levels, but also enhance neurodevelopment in children of supplemented mothers at 2 years of age.¹⁹¹ It is important to note that while studies have shown benefits using supplemental doses well above the RDAs for pregnancy and lactation (2.6-2.8 mcg/day), there is no set UL for vitamin B12 due to its low likelihood of toxicity, and therefore is safe at high doses.⁷⁷

There are currently no recommendations for vitamin B12 forms in prenatal supplements. The most commonly used supplemental form is cyanocobalamin, owed to its stability.¹⁹² However, the free vitamin B12 form must be further activated to the biologically active forms of vitamin B12, adenosylcobalamin (AdCbl) and methylcobalamin (MeCbl) which have distinct biological functions.¹⁹³ Thus, it has been postulated that supplementing with bioactive forms of vitamin B12 is preferred instead of the use of cyanocobalamin, due to reported enhanced bioavailability and safety.¹⁹² Additionally, some researchers posit that the use of active vitamin B12 forms may be preferred compared to cyanocobalamin to avoid the accretion of cyanide in tissues.¹⁹²

A recent in-vitro study examined the effects of different vitamin B12 forms in the presence of normal and supraphysiological concentrations of folic acid and found that combined MeCbl and AdCbl were superior in mitigating the effects of excess folic acid.¹⁹⁴ Additionally, a recent study applied in female Wistar rats compared forms of vitamin B12 in the presence of 400 mcg/day and 5 mg/day of folate on gestational outcomes. This study found that supplementation with the combined active forms of vitamin B12 significantly increased birth weights and modulated gestational outcome, and had better efficacy compared to other forms.¹⁹⁵

Deficiencies in vitamin B12 have been linked to intrauterine growth restriction, low birth weight, preterm birth, neural tube defects, and metabolic disturbances in offspring. Supplementing with vitamin B12 during pregnancy and lactation has been shown to improve vitamin B12 status, enhance infant neurodevelopment, and have potential benefits for

immune responses. While studies have demonstrated the advantages of using supplemental doses well above current recommendations, there is no set upper limit for vitamin B12 due to its low toxicity risk, making it safe at higher doses. Supplementation with the bioactive forms of vitamin B12, methylcobalamin and adenosylcobalamin, are likely preferable considering their safety and enhanced bioavailability.

Vitamin B6

Vitamin B6 levels decrease during pregnancy even when supplemented at the current dietary reference intake recommendations.^{196,197} Deficiencies in vitamin B6 have also been associated with increased risk for preterm birth, neurodevelopmental impairments in infants, and nausea and vomiting symptoms experienced during pregnancy.¹⁹⁸⁻²⁰⁰ This is unsurprising, as vitamin B6 is involved in several enzymatic reactions in the body, supporting a wide array of processes such as those related to one-carbon metabolism.¹⁰⁰ Several studies have suggested that additional vitamin B6 provision through supplementation in pregnancy may reduce the risk of preeclampsia and improve birth weight.^{201,202} Nausea is commonly experienced during pregnancy, and supplementation with vitamin B6 in doses of 10-50 mg/day, well above the RDA (1.9 mg/day), can reduce the severity of nausea symptoms.^{77,203-205} A recent meta-analysis also concluded that supplementation with vitamin B6, specifically pyridoxine, was beneficial for women suffering from nausea and vomiting in pregnancy.²⁰⁶ Additionally, some women who exhibit anemia during pregnancy do not respond to iron supplementation and may respond to vitamin B6 supplementation.²⁰⁷ Maternal supplementation with vitamin B6 also enhances concentrations of vitamin B6 in the breast milk and maternal intake is associated with infant vitamin B6 status.^{208,209}

However, the most common form for vitamin B6 in supplements, pyridoxine, is linked to toxicity at high doses.²¹⁰ In the US, the UL is set between 90-100 mg/day of vitamin B6 in pregnancy and lactation. However, it should be noted that this is based on reports of neurotoxicity at 200 to greater than 500 mg/day, so this UL was defined with some uncertainty.⁷⁷ However, supplementation with the active form of vitamin B6, pyridoxal-5'-phosphate (PLP), is not associated with toxicity or neuropathy.²¹¹ Thus PLP is a bioavailable and safe form of vitamin B6 which can be harnessed for supplementation for perinatal health. Moreover, an increase in the bioactive form of vitamin B6 in maternal circulation has been linked with DNA methylation levels of genes related to growth in the offspring and therefore may play a key role in fetal growth and development.²¹²

Deficiencies in vitamin B6 have been linked to preterm birth, neurodevelopmental impairments in infants, and pregnancy-related nausea and vomiting. Supplementing with vitamin B6, particularly the active form PLP during pregnancy can help reduce the risk of conditions like preeclampsia, improve birth weight, alleviate pregnancy-related nausea, and enhance infant vitamin B6 status. While the common form pyridoxine can be toxic at high doses, PLP is a safe and bioavailable alternative for supplementation during the perinatal period.

Riboflavin

Riboflavin is integral to various oxidation-reduction reactions and has two coenzyme forms, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD).⁷⁷ Riboflavin interacts with several nutrients such as iron, and is involved in energy and drug metabolism, growth and development, and supporting hematologic parameters.^{77,213} With regards to one-carbon metabolism, it has been demonstrated that FMN is necessary to generate the active vitamin B6 form PLP in tissues.^{214(p1)} Riboflavin also acts as a cofactor for MTHFR in folate recycling reactions.⁷⁷ In humans, those with a specific variant in MTHFR present with high circulating levels of homocysteine, which is exacerbated by low folate and riboflavin status.^{215,216} Additionally, polymorphisms in MTHFR have been linked to reduced folate metabolism and adverse health outcomes such as the development of hypertension in pregnancy.²¹⁷ This is interesting, as riboflavin deficiency has also been posited as a potential risk factor for preeclampsia.²¹⁸ Importantly, supplementation with riboflavin has been shown to increase PLP concentrations, and recent evidence suggests that riboflavin supplementation may help to reduce plasma homocysteine and blood pressure in hypertensive individuals with certain MTHFR genetic variants.²¹⁹⁻²²¹ Furthermore, riboflavin supplementation is well tolerated even at high doses.⁷⁷ In light of this evidence it is unfortunate that riboflavin status is rarely assessed in pregnancy, though evidence suggests that deficiency may be quite prevalent even in high-income countries.²¹⁴

Adequate riboflavin is necessary to generate the active form of vitamin B6 and support folate recycling reactions. Riboflavin supplementation is well tolerated at high doses and has the potential to reduce homocysteine levels and

blood pressure in individuals with specific MTHFR genetic variants. This is significant in the context of pregnancy, as the presence of certain MTHFR polymorphisms can lead to impairments in one-carbon metabolism and adverse pregnancy outcomes.

Choline

It cannot be understated that choline intake is critically essential during pregnancy and infancy to bolster neurodevelopment.²²² Choline is integral to methylation reactions, cell division, cellular signaling, the synthesis of neurotransmitters, and the development of the central nervous system.^{223,224} As stated previously, pregnancy and early life represent critically sensitive windows which shape health outcomes across the lifespan, with transgenerational impacts. During this window, the provision of large amounts of choline is particularly critical to support cognitive development and may also provide protection against neural and metabolic perturbations to the fetus.³⁸ As mentioned, choline is essential for methyl-group metabolism. For example, betaine, a choline derivative, is utilized in epigenetic modulation through DNA methylation.²²⁵ Thus, inadequate intake of choline can lead to lasting changes in protein synthesis and gene expression and ultimately health throughout the lifespan, via epigenetic modifications which occur in pregnancy.²²⁶

The findings of several animal studies support the adverse effects of choline deficiency and the positive impacts of choline provision on several maternal and offspring health outcomes. For example, maternal choline deficiency has been associated with impaired offspring brain development and angiogenesis, short-term memory deficits, and susceptibility to neurodevelopmental impacts of alcohol exposure.²²⁷⁻²²⁹ In contrast, prenatal choline supplementation demonstrates protective effects to offspring neurogenesis, neurodevelopment, and neurobehavioral outcomes associated with insufficient iron exposure.²³⁰⁻²³² Additionally, maternal choline supplementation has also been shown to ameliorate the effects of fetal alcohol exposure on neuronal function, and to improve neurocognitive function in murine models of Alzheimer's Disease and Down Syndrome while protecting the brain from the neuropathological changes associated with such conditions.^{230,233-237} Interestingly, maternal choline supplementation may also mitigate the effects of fetal brain damage associated with maternal immune activation through the attenuation of inflammatory cytokines, such as a decrease in fetal brain Interleukin-6, including that associated with coronavirus infection.^{238,239}

Importantly, methyl donors derived from choline are significantly reduced in pregnancy, through mechanisms in pregnancy which spare choline as well as upregulate utilization of choline-derived methyl donors for one-carbon metabolism.⁷⁸ Moreover, such loss cannot be compensated with intakes of folate. Further, concentrations of choline and phosphatidylcholine increase during pregnancy, given the essentiality of choline transfer to the fetus such that the child is born with choline levels higher than that of the mother.^{240,241} At present, the dietary reference intakes only recommend an AI for choline in pregnancy and lactation of 450 and 550 mg/day, respectively.⁷⁷ The pile of mounting evidence to suggest the insufficiency of these recommendations is staggering. Particularly concerning is that low maternal intakes of choline have been associated with higher risk for NTDs, and currently it is estimated that 90-95% of pregnant women do not meet this AI.^{22,242,243} Additionally, the presence of known genetic variants which impact choline metabolism compound this issue of suboptimal intake. Thus, it is evident that choline status and dietary requirements are a product of intricate interplay between life stage, nutrient interactions, and genetic variations.

To illustrate the impact of genetics of choline requirements, common loss-of-function variants in genes which regulate choline and folate metabolism, and thereby impact one-carbon metabolism, influence functional choline status and dietary choline requirements during conditions of deficiency and adequacy.^{224,244} While humans can produce choline endogenously, largely as phosphatidylcholine (PC) through the hepatic phosphatidylethanolamine N-methyltransferase (PEMT) pathway, endogenous human production of choline is not adequate to support metabolic needs.²⁴⁵ Common variants in the PEMT gene have been identified which result in the diminished synthesis of choline induced by the binding of the estrogen receptor to the estrogen response element in the promoter region of the PEMT gene, thus increasing dietary requirements.^{224,246} The commonality of such variants in PEMT may be particularly concerning for pregnant women, given the progressive elevations in estrogen during pregnancy, increasing the likelihood for augmented dietary choline needs.²²⁴ Furthermore, PEMT contributes to the hepatic export of DHA, as PC molecules derived from the PEMT pathway are enriched with long-chain omega-3 fatty acids.^{71,247} Thus, the provision of DHA to the fetus in pregnancy is critical and is dependent on the maternal PEMT pathway in this manner. Recently, an analysis of a choline intervention trial of women entering their second trimester of pregnancy found that maternal variants in PEMT resulted in lower maternal RBC DHA during pregnancy and lower cord RBC DHA at delivery.⁷¹

RBC DHA during pregnancy and lower cord RBC DHA at delivery.⁷¹

Further, critical appraisals of the evidence have suggested that high maternal choline intakes, up to 1 g/day, during pregnancy are safe and may exert additional benefits on neurodevelopment and cognitive function.^{248–250} Increasing levels of choline intake during pregnancy can increase choline-derived methyl donors in circulation and improve placental DNA methylation patterns.^{240,251} Choline supplementation may also curb the adverse metabolic outcomes which result from genetic variations in methyl-donor metabolism.²⁵² Several studies have examined the effects of choline supplementation in doses near the AI to much higher doses during pregnancy on maternal and child health outcomes. One study found that children of mothers who received 930 mg/day of choline during pregnancy, had 33% lower circulating cortisol levels compared to those whose mothers received 480 mg/day of choline.²⁵¹ A recent study which compared the effects of similar doses (480 mg/day vs 930 mg/day) of choline in late pregnancy, found that children at 1 year of age had significantly increased information processing speeds when their mothers consumed 930 mg/day of choline.²⁵⁰ Results from a randomized controlled feeding study in which pregnant women consumed either 480 mg/day or 930 mg/day of choline during the 3rd trimester found that offspring of mothers who received 930 mg/day of choline had improvements in sustained attention assessed at 7 years follow-up compared to those exposed to 480 mg/day.²⁴⁹ Thus, evidence to support a higher dose of perinatal choline supplementation to support neurocognition is compelling. Additionally, during lactation demands for choline to the infant increase and higher levels of maternal choline intake have been shown to enhance the choline concentrations in human milk.²⁵³ Further, recent studies suggest that higher doses of choline supplementation during pregnancy may favorably modulate circulating and placental risk markers for preeclampsia, suggesting that greater intakes of choline are also supportive for maternal health and perinatal outcomes.²⁵⁴ Overall this body of evidence asserts that in order to optimize maternal and child health outcomes, 930 mg/day of choline is superior to the current AI.

It is imperative to note that the UL for choline is 3500 mg/day, and high doses of choline (930 mg/day) in pregnancy have been shown to improve markers of choline metabolism with no adverse reactions.⁷⁷ Currently, most prenatal supplements do not contain adequate amounts of choline, or any choline at all.²²³ This is occurring in the face of support from leading health organizations such as the American Medical Association for the provision of choline in prenatal vitamins.^{255,256} Additionally, there is evidence from studies in women of childbearing age which suggest that increasing choline intake may synergistically augment hepatic export of DHA, and therefore may improve DHA provision to the fetus. Indeed, prenatal choline supplementation has been shown to enhance hepatic DHA export and DHA status biomarkers via supporting methyl group supply in pregnant women also receiving supplemental DHA.²⁵⁷ Therefore, strategies which seek to complex DHA with choline may confer synergistic benefits particularly in women with low DHA status.

The AI of 450 mg/day choline for pregnancy was ultimately derived from evidence regarding the amount of choline necessary to prevent liver dysfunction in men and not with respect to pregnancy or offspring outcomes. Research indicates that higher doses of choline supplementation, up to 930 mg/day, during pregnancy can improve offspring neurocognitive outcomes and improve risk markers of preeclampsia. Many prenatal supplements do not provide adequate choline, despite recommendations from leading health organizations. Additionally, increasing choline intake may enhance the delivery of essential fatty acids like DHA to the fetus, which is crucial for brain development.

Micronutrients - Vitamins

Vitamin D

The sufficiency of maternal vitamin D status during pregnancy is essential, as the mother is the source of all vitamin D for the fetus via placental transfer. Adequate provision of vitamin D supports maternal immune function, bone health, calcium homeostasis, and blood pressure.^{258–261} Additionally, maternal vitamin D status directly impacts fetal status and therefore is vital to support enamel formation, bone mineralization, immune system development, cellular division, and lung maturation.^{259,262–265} Maternal deficiencies in vitamin D have been associated with preterm birth and adverse neurodevelopmental and immunological outcomes.^{266–268} In contrast, vitamin D supplementation has been shown to reduce the risk of preterm birth, preeclampsia, and GDM.^{261,269,270} Vitamin D can influence immune and inflammatory responses and it has been demonstrated that its immune modulating mechanisms influence fertilization, implantation, and maintenance of pregnancy.^{258,271} Low vitamin D status has also been linked to pregnancy loss and maternal tolerance for implantation in women with recurrent implantation failure.^{272–274}

Evidence suggests that vitamin D deficiency is common in pregnancy, and risk for deficiency is impacted by several factors including sun exposure, season, geographical location, body mass index, and skin pigmentation.²⁷⁵ Though there are present racial/ethnic differences in vitamin D status, a recent study demonstrated that both black and white pregnant women and neonates living in the US are at high risk for deficiency, regardless of the reporting of additional vitamin D supplementation.²⁷⁶ The findings of this study suggested that pregnant women in the US likely require higher doses of vitamin D supplementation to improve maternal and child status. Additionally, breastfed infants may be more susceptible to vitamin D insufficiency than formula fed infants due to poor maternal status or low content of vitamin D in human milk.²⁶² Moreover, vitamin D composition in breast milk is affected by maternal vitamin D intake and status, sun exposure, body mass, and genetics and it is likely that mothers will require higher doses of vitamin D to support adequate concentrations in breastfed infants.^{262,277}

The current RDA for vitamin D in pregnancy was updated in 2011 and is set to 600 IU per day in order to achieve a status of >50 nmol/L 25-hydroxyvitamin D (25[OH]D).¹⁷ However, many researchers and clinicians suggest that a status of 50 nmol/L is not adequate to achieve benefits in pregnancy related outcomes, and 75 nmol/L may be a more appropriate reference.²⁷⁸ Higher doses of vitamin D, upwards of 2000 IU are needed to achieve such circulating levels of 25(OH)D in pregnant women.^{258,279,280} Additionally, pregnancy outcomes were not considered as indicators for setting the current vitamin D recommendations in pregnancy. Instead, the current reference intakes do not differ between pregnant and lactating women and age matched adults, on the basis that evidence did not support an association between vitamin D status and bone mass in pregnancy or between vitamin D and bone mineral density or the composition of human milk in lactation.¹⁷ These recommendations are inherently flawed, as it is necessary to consider population specific outcomes when determining nutrient reference intakes, and several studies have supported the role of vitamin D in maternal and child outcomes far beyond bone density.²⁸¹

However, a recent study did find that sufficient vitamin D concentrations in children enhance bone mineralization at 6 years of age, which was further augmented when mothers received high doses of vitamin D prenatally.²⁸² The combination reduced the risk of fractures in childhood by 60% in this study, which could confer reductions in risk for osteoporosis. Strikingly, a recent double-blind randomized controlled trial found that offspring of mothers who received high dose vitamin D in the third trimester had a 50% lower odds of enamel defects measured at 6 years of age.²⁸³ This finding lends crucial support to the importance of in-utero vitamin D exposures on fetal enamel formation and dental health in later life.²⁸³ Moreover, it has been demonstrated that vitamin D supplementation at higher doses of 4000 IU/day in pregnancy is associated with no adverse reactions and is sufficient to attain adequate vitamin D status and calcium homeostasis in pregnant women, regardless of race.²⁸⁰ It has been suggested that vitamin D supplementation is able to improve maternal and child health outcomes across diverse racial and ethnic groups when a higher level is achieved, particularly when the serum levels of circulating 25(OH)D reach levels >40 ng/mL.²⁸¹ Infant cord blood 25(OH)D levels reflect 50-80% of maternal serum 25(OH)D levels, thus by reaching optimal maternal serum vitamin D levels, we enhance in utero vitamin D transfer. Additionally, it seems that the greatest change is achieved at 6-8 weeks from when supplementation is introduced.²⁸⁴ Thus, the dosage and time frame for initiating vitamin D supplementation are both crucial given that vitamin D exerts genomic actions on the placenta and influences inflammation in the placenta.²⁸⁵

Deficiencies in vitamin D have been associated with pregnancy loss, preterm birth, adverse neurodevelopmental and immunological outcomes, and an increased risk of pregnancy complications. Vitamin D supplementation, especially at higher doses, has been shown to reduce the risk of preterm birth, preeclampsia, and gestational diabetes, and can have lasting positive effects on offspring, including improved bone mineralization and dental health. Diverse pregnant women are at risk for deficiency, and higher doses of vitamin D, at or above 2000 IU, are needed to achieve optimal circulating levels for maternal and child health, with some studies suggesting that levels above 40 ng/mL are ideal.

Vitamin A

Though there is widespread lack of consistent guidance regarding dietary supplementation during pregnancy, vitamin A is associated with much contention regarding its use in prenatal supplements.²⁸⁶ Most ubiquitously, the provitamin A carotenoid beta-carotene is included in prenatal supplements in lieu of preformed vitamin A. This hesitation to supplement with vitamin A is linked to the perceived risks of vitamin A teratogenicity, though in reality this risk is present yet overstated.²⁸⁶⁻²⁸⁸ A study of about 23,000 pregnant women suggested a threshold of 3,000 mcg RE/day, the current UL in the US, though many other studies have suggested the safe level is likely higher up to 9,000 mcg RE/day.

day.²⁸⁹⁻²⁹¹ Vitamin A is essential to the developing embryo and deficiencies in vitamin A can result in modifications to gene expression which impair development.^{288,289,292} Vitamin A is also key to organogenesis and immune function, and deficiencies in vitamin A may increase the risk for infectious diseases and respiratory illness in infants.^{288,292,293}

A study published in 2010 examined lung function in 9-13 year old offspring whose mothers received vitamin A or beta-carotene before, during, and after pregnancy, and found improvements in child lung function in those with mothers who received vitamin A and was not observed in mothers who received beta-carotene.²⁹³ However, a meta-analysis noted that vitamin A or beta-carotene supplementation may significantly improve hemoglobin levels and reduce risk of anemia.²⁹⁴ An assessment of rural Bangladeshi children from two trials found that prenatal and postnatal supplementation with vitamin A was associated with improvements in domains of executive function in children analyzed at 8 years of age.²⁹⁵ Additionally, a study examining a food fortification strategy in Denmark which increased the amount of vitamin A in margarine, as retinol and beta-carotene, found that increased consumption of vitamin A by the mother during pregnancy was associated with a reduced risk of offspring development of type 2 diabetes in adulthood.²⁹⁶ It is important to note the availability and conversion of beta-carotene to active vitamin A exhibits a high level of variability and is affected by individual factors, such as vitamin A status and genetic variants associated with the metabolism of beta-carotene, as well as the food matrix.²⁹⁷ As mentioned previously, SNPs have been identified in genes, such as BCMO1, which modify beta-carotene absorption and conversion, and thereby responsiveness to beta-carotene supplementation.⁷⁰ Therefore, the narrative which asserts the teratogenicity of preformed vitamin A, even consumed at safe doses, has resulted in its removal or complete replacement with beta-carotene in most prenatal supplements. However, consuming provitamin A carotenoids, such as beta-carotene, as the only means of vitamin A supplementation may be met with limited conversion in many mothers. Given the importance of vitamin A in development, a combination of preformed vitamin A and beta carotene is optimized to confer benefits and mitigate deficiencies.^{70,298}

The use of Vitamin A in prenatal supplements is a topic of debate, with concerns about teratogenicity leading to the inclusion of beta-carotene (provitamin A) instead of preformed vitamin A in many supplements. However, studies have suggested that this risk is likely overstated and vitamin A is essential for the developing embryo and organogenesis. Vitamin A supplementation, including preformed vitamin A, may improve lung function in offspring, reduce the risk of anemia, and positively impact executive function in children. It's important to note that beta-carotene conversion to active vitamin A varies among individuals and may not be sufficient for some pregnant women, highlighting the importance of a combination of preformed vitamin A and beta-carotene for optimal benefits.

Vitamin C

Vitamin C is a potent antioxidant which provides protection from oxidative stress and plays an essential role in collagen crosslinking.²⁹⁹ The risk of vitamin C deficiency is increased for vulnerable groups such as pregnant and lactating women, and it has been shown that vitamin C levels decrease in pregnancy if not supplemented, likely due to hemodilution and increased fetal transfer.^{300,301} In breast milk composition, vitamin C is highest in colostrum and then stabilizes in mature milk, requiring a continuous maternal supply to ensure presence within the mature milk due to its solubility.^{302,303} The current recommended intakes for pregnancy and lactation are set to 85 mg/day and 120 mg/day, respectively, in the US although there is evidence which supports that a vitamin C intake of 400 mg/day is necessary to reach optimal plasma vitamin C concentrations.^{304,305} Vitamin C deficiencies in pregnancy may be associated with premature rupture of membranes and preterm deliveries.³⁰⁶ However, studies have found that vitamin C supplementation reduces incidence of premature rupture of membranes and the risk for preterm birth.²⁹⁹ A study completed in Turkey examined the effects of vitamins C (1000 mg/day) and E (400 mg/day) supplementation during pregnancy, and found that women receiving the supplement remained pregnant longer in the instance of premature rupture of membranes, compared to the control.³⁰⁷ Additionally, supplementation with vitamin C has also been shown to reduce the risk of urinary tract infection during pregnancy.³⁰⁸ Notably, it has been recently reported that vitamin C functions in epigenetic regulation through DNA and histone demethylation, and may also be key to fetal and postnatal development.³⁰⁹ Thus, the current RDA is likely insufficient to achieve optimal concentrations of vitamin C in pregnancy.

Pregnant and lactating women are at increased risk of vitamin C deficiency, which can have adverse effects on pregnancy outcomes. While the current vitamin C recommendations in the US for pregnancy and lactation are 85 mg/day and 120 mg/day, respectively, evidence suggests that a higher intake is needed to achieve optimal plasma vitamin C levels. Deficiencies in pregnancy have been associated with issues like premature rupture of membranes and preterm

deliveries, but vitamin C supplementation has been shown to reduce these risks and may also play a role in epigenetic regulation and thereby development.

Vitamin E

Infants experience a multitude of exposures which can induce oxidative stress, and therefore requirements for antioxidant nutrients, such as vitamin E, during pregnancy are elevated. Low concentrations of vitamin E in pregnancy have been associated with increased risk for SGA, preeclampsia, and GDM.³¹⁰⁻³¹² It has also been demonstrated the vitamin E may be beneficial in the prevention of asthma and wheezing in children when supplemented with 8-18 mg/day.³¹³ However, a higher dose of vitamin E at 100 mg/day was shown to reduce pregnancy related leg cramps.³¹⁴ Recent studies have demonstrated that women with low vitamin E concentrations of < 7.3 mg/L had increased risk of preeclampsia in the first trimester of pregnancy, thus supplementation with vitamin E in pregnancy may be protective against preeclampsia.³¹¹ It should also be noted that the UL for vitamin E is 1000 mg/day, and no adverse events have been noted in high quality clinical trials.³⁰⁴ A recent report also suggested that vitamin E supplementation, as alpha tocopherol, may benefit from formulation with mixed tocopherols as is present in the diet to optimize antioxidant capacity.³¹⁵

Low vitamin E levels during pregnancy have been linked to higher risks of conditions like small for gestational age, preeclampsia, and gestational diabetes. Vitamin E supplementation can have various benefits, such as reducing pregnancy-related leg cramps. A recent report suggests that formulating vitamin E supplements with mixed tocopherols, similar to dietary sources, may optimize antioxidant capacity.

Biotin

Biotin is critical for several enzymes involved in nutrient metabolism.³¹⁶ Although symptomatic biotin deficiency is rare, pregnancy may result in reduced biotin status with increased excretion of 3-hydroxyisovaleric acid.³¹⁷ Recent studies have reported that suboptimal biotin status is present in about 50% of pregnancies, which may negatively impact fetal development.^{316,317} Indeed, it has been suggested that even the marginal biotin deficiencies that develop in normal pregnancy may be teratogenic.³¹⁸ Thus, there is evidence to support that biotin intake in pregnancy and lactation may be necessary in excess of current recommendations to support perinatal requirements.³¹⁶ Additionally, biotin is produced by gut microbiota and biotin deficiencies have been associated with dysbiosis and inflammation, which may exacerbate deficiency related outcomes.³¹⁹ However, short term biotin supplementation with 300 mcg/day has been shown to recover biotin status in pregnancy.³¹⁷ Notably this dose is considerably above the current AI for pregnancy of 30 mcg/day.⁷⁷ Considering that there exists no evidence to support biotin toxicity, even at high intravenous doses of 20 mg/day individuals with biotinidase deficiency, supplementation in pregnancy is a key strategy to improve biotin status.⁷⁷

Recent studies indicate that suboptimal biotin status is prevalent in around 50% of pregnancies, which could have negative impacts on fetal health. Biotin intake during pregnancy and lactation above current recommendations is likely needed to ensure adequate levels and support perinatal requirements. Short-term biotin supplementation of 300 mcg/day has been effective in restoring biotin status in pregnancy, though this dose is substantially higher than the current AI for pregnancy of 30 mcg/day. Notably, biotin supplementation has shown no evidence of toxicity, making it a crucial strategy to improve biotin status in pregnancy.

Pantothenic Acid

Pantothenic acid is necessary for the synthesis and maintenance of coenzyme A, which is centrally involved in macronutrient metabolism in the body.⁷⁷ Concentrations of pantothenic acid are reduced in pregnancy, and while reporting of pantothenic acid intakes at the population level is scarce, it has been demonstrated that women consume less than the AI for pantothenic acid.^{320,321} This suggests that supplementation is likely beneficial to improve pantothenic acid status in pregnancy. Importantly, there is no UL for pantothenic acid, due to the lack of toxicity reporting in the literature even at high intakes.⁷⁷

Pantothenic acid levels decrease during pregnancy, and women often consume less than the recommended intake. Consequently, supplementation to enhance pantothenic acid status in pregnancy is likely beneficial, and its lack of reported toxicity even at high doses makes it a safe option.

Thiamin

Thiamin is necessary for a multitude of biological processes including macronutrient metabolism, the synthesis of amino acids and neurotransmitters, and maintenance of tense muscle function.^{322,323} Suboptimal maternal intakes or status of thiamin during pregnancy and lactation place infants at increased risk for thiamin deficiency.³²⁴ Additionally, the developing fetus will receive thiamin at the expense of the mother via placental transfer, and thus maternal insufficiencies are at risk of exacerbation in perinatal periods.³²⁵ During pregnancy, it has been noted that thiamin levels decrease, possibly by up to 40%.^{326,327} Further, studies have found that among pregnant women consuming thiamin through a multivitamin supplement containing 3 mg of thiamin, over 17% presented with a thiamin deficiency.³²⁶ However, prenatal supplementation with thiamin can improve maternal intakes which may confer benefits to maternal health and glycemia.³²⁸ Animal studies have demonstrated that thiamin deficiency can impair glucose tolerance.³²⁹ In support of the role of thiamin in maintenance of glucose metabolism, a recent analysis of the Tonji Birth Cohort, which included over 3,000 pregnant women, found that mothers with higher thiamin intakes during pregnancy exhibited a lower risk of GDM.³²³

Thiamin becomes particularly important during pregnancy and lactation. Studies have reported a significant reduction in thiamin levels, possibly up to 40%, during pregnancy. Thiamin supplementation during pregnancy not only helps improve maternal thiamin intake but also has the potential to benefit maternal health and glycemic control, potentially reducing the risk of gestational diabetes.

Vitamin K

Vitamin K is required for the function of enzymes involved in hemostasis and is also essential for bone modeling via direct and indirect mechanisms.^{330,331} However, vitamin K encompasses a family of compounds, including phyloquinone or vitamin K1 and several subtypes of menaquinones or vitamin K2. The isoforms of vitamin K vary in food source, bioavailability, and half life.³³² Vitamin K1 is the primary form of vitamin K found in green leafy vegetables and vitamin K2 is present in animal products and fermented food, as vitamin K2 is largely produced by bacteria.^{333,334} As such, most menaquinones are also produced in the human gut by resident microbiota.³³⁵ The current RDA for vitamin K in pregnancy and lactation is 90 mcg, however these recommendations are based on vitamin K1 intake in adults.²⁹⁰ Interestingly, it has been found that menaquinone-7 (MK-7) has a longer half-life of 72 hours with improved absorption, bioavailability, and carboxylation efficacy compared to vitamin K1.^{332,336}

Emerging evidence has suggested that vitamin K2 demands particular recommendations.³³² This assertion is based on research investigating vitamin K2 which suggests that higher intakes enhance bone quality, reduce fracture risk and mitigate blood vessel calcification, while studies examining supplementation with vitamin K1 often find null results regarding bone health.³³⁷⁻³⁴⁰ In postmenopausal women, supplementation with 180 mcg/day of vitamin K2, specifically MK-7, for three years was associated with an attenuated decline in bone mineral density and bone strength.³⁴¹ Another randomized controlled trial in healthy postmenopausal women found that a similar dose of MK-7 supplementation for three years improved indices of arterial stiffness.³⁴² Additionally, a case series found that 45 mcg/day of vitamin K2 was a safe option to improve pregnancy-associated osteoporosis.³⁴³ Importantly, recent evidence suggests that menaquinones in the human gut are quite variable and impacted by the microbial composition of the gastrointestinal tract.³⁴⁴ Given the profound influence of the obesogenic environment on inflammatory mechanisms and dysbiosis, vitamin K2 supplementation may be further supported given the contribution of bacteria to its production. It is also relevant to note that there is no UL currently in place for vitamin K.²⁹⁰ A recent review also suggested that the use of vitamin D and vitamin K2 may be a favorable strategy to treat osteoporosis, suggesting the benefit of combined supplementation.³⁴⁵

Vitamin K is crucial for both blood clotting and bone health and exists in various forms, with vitamin K1 primarily found in green leafy vegetables and K2 in animal and fermented foods. Emerging evidence indicates that vitamin K2, particularly MK-7, exhibits superior absorption and offers benefits for bone quality, reducing fracture risk, and mitigating blood vessel calcification, while vitamin K1 supplementation often shows limited impact on bone health. Vitamin K2's effects are influenced by gut microbiota composition, and its supplementation, alongside vitamin D, may be a promising approach for osteoporosis treatment, with no established upper limit for vitamin K intake.

Micronutrients - Essential Trace Elements

Iron

During pregnancy, the prevalence of iron deficiency increases, which may be related to the woman's preconception iron status as well as the bioavailability of iron consumed from food products. Maintenance of iron status during gestation is central to sustain increased iron requirements which support expansion of RBC mass, placental provision of iron, and adequate transfer to the fetus.³⁴⁶ Thus, it has been noted that gestational requirements increase needs for iron by an additional 1 g.³⁴⁶ Additionally, iron-deficiency anemia early in pregnancy increases the risk for preterm birth and iron deficiency in offspring.^{347,348} However, iron needs are lower in lactation, as iron concentrations are low in human milk and breastfeeding women are usually amenorrheic.³⁴⁹ Iron supplementation in pregnancy has been shown to improve birth outcomes, possibly via modulation of erythropoiesis.³⁵⁰ In a review of randomized controlled trials, including over 43,000 pregnant women, iron supplementation was associated with reduced risk of anemia and iron deficiency in pregnancy.³⁵¹ The findings also suggest that iron supplementation may improve birth outcomes.³⁵¹

However, there is a question regarding optimal levels of forms of iron supplementation in pregnancy. It has been noted that deficiencies and excesses in iron status can impair health outcomes, such that a U-shaped curve has been demonstrated between maternal hemoglobin status and adverse outcomes including SGA and preterm birth.³⁵² These associations seem to be particularly poignant when low hemoglobin is present in early pregnancy.³⁵² Studies have shown that iron supplementation may be most effectively dosed using information related to baseline iron status assessed via circulating ferritin concentrations which reflect iron stores.³⁵³ Recent evidence suggests that adjusting iron dosing according to ferritin status in early pregnancy also provides maximal protection against anemia and iron deficiency in pregnant women.^{353,354} Iron dosing strategies must also consider that iron bioavailability may be inhibited by the presence of other food components, such as calcium, zinc, phytic acids, and polyphenols.³⁵⁵⁻³⁵⁸

Iron salts, such as ferrous sulfate and ferrous fumarate, are commonly used in supplement formulas however exhibit low bioavailability due to low absorption in the intestine and dietary components such as phytates which limit absorption.⁸⁴ Ferrous iron may also cause irritation to the gastrointestinal tract lining and result in side effects such as nausea and abdominal pain.³⁵⁹ Amino acid chelates have arisen as effective supplemental forms of nutritive minerals, which can facilitate absorption and improve bioavailability.^{84,360} Ferrous bisglycinate is an amino acid iron chelate with increased bioavailability compared to iron salts and has been shown to mitigate gastrointestinal side effects of iron supplementation.³⁶⁰ A recent systematic review and meta-analysis compared iron supplemental forms, including ferrous bisglycinate in pregnant women. The findings demonstrated that supplementation with ferrous bisglycinate for 4-20 weeks led to elevated heme concentrations in pregnant women compared to other iron forms.⁸⁴ Pregnant women in the study also reported significantly fewer adverse gastrointestinal events during the trial. Lower doses of iron amino acid chelates have also been shown to be more advantageous for treating iron deficiency in pregnancy than ferrous sulfate at higher doses.^{360,361} Taken together the evidence suggests that while iron supplementation is beneficial in pregnancy, early pregnancy iron status should be considered in dosing recommendations and amino acid chelates are optimized forms for exerting effective results even at lower doses.

Pregnancy leads to an increased risk of iron deficiency, and research suggests that iron supplementation during pregnancy can improve birth outcomes and reduce the risk of anemia, particularly when the iron form is optimized for absorption and minimal side effects. Adjusting iron dosing based on ferritin status, considering bioavailability factors, and using iron amino acid chelates like ferrous bisglycinate are effective strategies for addressing iron deficiency in pregnancy and enhancing maternal and fetal health.

Calcium

Pregnancy places high demands on calcium due to the needs for fetal growth.^{362,363} Though calcium absorption rises during pregnancy, adequate maternal dietary intake is vital to support elevated needs, as absorption is directly correlated with dietary intake during gestation.^{363,364} Inadequate calcium intake during pregnancy may confer adverse outcomes to both the mother, such as preeclampsia, and the developing fetus including low birth weight, diminished bone mineralization, and preterm birth.³⁶⁵⁻³⁶⁹ If dietary intake of calcium is low, calcium may be released from maternal bone to compensate and allow for mineralization of bone for the fetus, which could result in reduced maternal and offspring bone

bone mineral density.³⁶³ Additionally, a low occurrence of preeclampsia has been historically noted in populations with higher levels of calcium intake, which has been supported by accumulated epidemiological and clinical evidence.^{370,371} Hypocalcemia has indeed been linked to preeclampsia, as has low dietary milk intake.^{372,373} These findings catalyzed research to examine whether increased calcium through supplementation during pregnancy has the potential to reduce risk for preeclampsia. Several studies have examined the use of calcium supplementation, and a recent Cochrane systematic review reported that both high dose (1g/day) and low dose calcium supplementation of around 500 mg/day in the second half of pregnancy are associated with a reduction in preeclampsia.³⁷⁰ This is especially promising, as calcium supplementation is safe in pregnancy and there is evidence that supplementation may also reduce risk of hypertension in offspring.³⁷⁴

Inadequate maternal calcium intake may lead to adverse outcomes, such as preeclampsia, low birth weight, and reduced bone mineralization. Research supports that calcium supplementation, whether with high or low doses, can reduce the risk of preeclampsia during pregnancy while also being safe for both the mother and the offspring.

Selenium

Maternal and fetal oxygen consumption increase during pregnancy, which increases the generation of reactive oxygen species.³⁷⁵ Thus, it is reported that gestation is a period of heightened oxidative stress, which may be further exacerbated in conditions such as GDM and preeclampsia.^{376,377} Selenium is a micronutrient which possesses antioxidant properties that serve to prevent cellular damage. Selenium is central to the synthesis of selenoenzymes, including glutathione peroxidases and thioredoxin reductases, which function in antioxidant systems to limit oxidative insults and modulate inflammatory responses.^{378,379} It has been reported that circulating concentrations of selenium and glutathione peroxidase decrease during pregnancy, due to hemodilution and augmented transport to the fetus.^{380,381} Selenium deficiency has been associated with impaired development, preeclampsia, GDM, miscarriage, preterm delivery, and infertility.^{378,382–385} Low maternal selenium status may adversely impact oxidative balance as well as inflammatory, immune, and metabolic processes which can impair fetal programming.^{382,386} Hence, antioxidant defense mechanisms are central to maternal and fetal health, and maternal supplementation with antioxidants may enhance resistance to oxidative stress.

Therefore, selenium supplementation has been widely investigated to examine its impact on maternal and fetal outcomes. Importantly, selenium's antioxidant properties have been linked to improvements in embryonic development.³⁸⁷ A meta-analysis found that selenium supplementation in pregnancy led to significant reductions in the incidence of preeclampsia.³⁸⁸ Interestingly, maternal essential trace element status has also been implicated in offspring outcomes. A recent study found that maternal erythrocyte selenium and manganese levels sampled after delivery were inversely associated with offspring systolic blood pressure at 3 to 15 years of age.³⁸⁹ Further, a recent randomized controlled trial aimed to assess the effects of 200 mcg/day of selenium supplementation during pregnancy in women with GDM, and found that selenium supplementation significantly increased expression of genes involved in glucose and lipid metabolism and decreased risk of newborn hospitalization.³⁹⁰ Moreover, selenium supplementation of 200 mcg/day in pregnancy and postpartum has also been demonstrated to lower thyroid inflammation and reduced incidence of hypothyroidism in women predisposed to postpartum thyroid dysfunction.³⁹¹ Of note, selenium supplementation during pregnancy, beginning in the first trimester, was shown to increase circulating selenium and significantly decrease Edinburgh Postnatal Depression Scale scores in the treatment group compared to the control.³⁹² Though the RDA is 60-70 mcg/day for pregnancy and lactation, these studies suggest that supplemental selenium above this recommendation exhibits key benefits to maternal and child health.

Selenium supplementation during pregnancy has been associated with various benefits, such as reducing the risk of preeclampsia, improving embryonic development, enhancing expression of genes involved in glucose and lipid metabolism in women with GDM, and decreasing the incidence of postpartum thyroid dysfunction. These findings highlight the importance of antioxidant defense mechanisms in promoting maternal and fetal health and suggest that selenium supplementation beyond the recommended daily intake can offer significant advantages.

Magnesium

Magnesium is an abundant essential trace mineral and acts as a cofactor in over 600 enzymatic reactions which support a multitude of biological functions.^{393,394} This metal ion is essential to neuromuscular activity, nucleic acid and protein synthesis, energy metabolism, bone formation, and immune system support.³⁹³ Strikingly, it has been reported that around 50% of Americans have an estimated magnesium intake that is considered inadequate, and a recent study suggested that nearly 48% of pregnant women consume less than the EAR for magnesium even with supplement use.^{22,395} Importantly, magnesium requirements increase in the perinatal period. Thus, an RDA of 350–400 mg/day is recommended in pregnancy and 310–360 mg/day during lactation, compared with 300–310 mg/day for non-pregnant or non-lactating women, reflecting about a 10% increase in needs.³⁹⁶

Magnesium status may influence maternal health outcomes as well as fetal growth and development during gestation. Preclinical evidence has also demonstrated that maternal hypomagnesemia may be associated with fetal growth restriction.³⁹⁷ Moreover, there is evidence to suggest that magnesium deficiency can augment the risk for preeclampsia and preterm birth via deficiency-associated uterine muscle hyperexcitability.^{398,399} Though the role of magnesium in GDM is controversial, a recent systematic review and meta-analysis also reported that serum magnesium levels were lower in women with GDM than in healthy pregnant women.⁴⁰⁰ Contrastingly, higher serum magnesium in pregnancy has been associated with lower incidence of preeclampsia and GDM.³⁹³ Importantly, it has been posited that magnesium may influence fetal programming and subsequent disease risk throughout the lifespan.³⁹⁶ The consequences of low serum and dietary magnesium intake include demonstrated associations with adverse health outcomes including cardiovascular disease, type 2 diabetes mellitus, and hypertension.⁴⁰¹

Results from animal studies suggest that maternal magnesium supplementation can attenuate intrauterine growth restriction.⁴⁰² Moreover, a recent systematic review and meta-analysis which analyzed data from randomized controlled trials, including 3068 pregnant women and 352 preterm infants, found that the rate of preterm birth was reduced for women in the magnesium supplementation group compared with women in the control group.³⁹⁸ There is also evidence to suggest that magnesium supplementation in pregnancy may improve parameters related to glucose control in GDM.⁴⁰³ Magnesium is also administered to support neuroprotection prior to very preterm delivery.⁴⁰⁴

Magnesium is an essential mineral with a wide range of biological functions, and its requirements increase during pregnancy and lactation. Adequate magnesium intake during pregnancy is crucial as it can influence maternal health outcomes, fetal growth, and the risk of conditions like preeclampsia, preterm birth, and gestational diabetes. Recent studies suggest that magnesium supplementation in pregnancy may help reduce the rate of preterm birth and improve glucose control in gestational diabetes.

Zinc & Copper

Zinc is an essential trace element required for hundreds of enzymatic reactions involved in several physiological processes.⁴⁰⁵ Zinc is crucial for growth, development and embryogenesis in pregnancy, and zinc dependent processes are key to gene transcription and cell proliferation.⁴⁰⁶ While zinc deficiency is considered rare, recent evidence suggests a substantial portion of pregnant women may have inadequate zinc intakes even with dietary supplementation.^{22,407} Zinc deficiency can impede growth and development, particularly neonatal brain development and a recent umbrella review and meta-analysis found an association between low zinc status and pregnancy complications.^{406,408,409} Additionally, it has been demonstrated that zinc deficiency may increase the risk of SGA.⁴⁰⁶ Fortunately, zinc supplementation has been shown to reduce the risk of preterm birth and increasing zinc intake to adequate levels may thwart teratogenesis.^{409,410} Clinical trials which have examined 30 mg of zinc supplementation, have found that zinc reduces c-reactive protein and improves total antioxidant capacity levels and glycemia in women with GDM.^{411,412} The recommended intake for zinc is 11 mg/day during pregnancy in the US, although research suggests that those following plant-based diets may require up to 50% more zinc due to high phytate content in such diets.^{290,413,414}

Copper is an essential mineral which functions as a cofactor for antioxidant enzymes which plays a role in immune, inflammatory, and neurochemical processes.⁴¹⁵ It has also been noted that maternal concentrations of copper rise in pregnancy.⁴¹⁶ Importantly, deficiencies and aberrant increases in circulating copper have been associated with adverse maternal health outcomes, including pregnancy-induced hypertension.^{417,418} Recent evidence suggests that lower copper may be associated with diminished antioxidant activity and higher risk pregnancy-induced hypertension.⁴¹⁵

Higher pre-pregnancy Body Mass Index (BMI) was found to influence the estimates in this study, specifically, a pre-pregnancy BMI ≥ 25 kg/m² is associated with significantly higher serum copper concentrations in the 10–14th pregnancy week, which could mask deficiency.⁴¹⁵ Thus, the impact of BMI on the serum copper levels should likely be factored into assessments.

Importantly, zinc and copper supplementation in tandem have been suggested to balance absorption of both nutrients, with a zinc to copper ratio of 15:1 asserted as optimal by many integrative and alternative practitioners. The balance attained by this ratio of intake is particularly important, as excess copper during pregnancy has also been associated with elevated risk of glucose dysregulation.⁴¹⁹ Additionally, a recent case-control study of individuals with major depressive disorder, found significantly lower levels of zinc and increased concentrations of copper in cases compared to controls.⁴²⁰

With respect to pregnancy, a recent study demonstrated that a higher copper to zinc ratio in plasma was associated with the development of pregnancy-specific distress symptoms throughout gestation.⁴²¹ Interestingly, postpartum zinc supplementation has also been shown to improve the status of maternal blood zinc levels and decrease the risk of developing PPD.⁴²²

Zinc deficiency can impede neonatal brain development and may increase the risk of small for gestational age babies. Zinc supplementation has shown promise in reducing the risk of preterm birth and improving antioxidant levels and glycemia in women with gestational diabetes. Postpartum zinc supplementation has also shown benefits in improving maternal blood zinc levels and reducing the risk of postpartum depression.

Though maternal copper levels rise during pregnancy, both copper deficiency and excessive levels have been associated with adverse maternal health outcomes, including preeclampsia and pregnancy-induced hypertension. Imbalances, particularly excess copper, have been linked to glucose dysregulation and pregnancy-specific distress symptoms. Balancing zinc and copper intake, with a ratio of 15:1, is recommended to optimize absorption and outcomes.

Manganese

Manganese is one of the most abundant essential trace elements, known to be essential for multitude enzymatic reactions and is involved in the metabolism, glucose regulation, bone formation, hemostasis, immune function, cognitive function, and reproduction.^{290,423–427} Animal studies examining the effects of severe manganese deficiency have found associations with impairments to growth and bone malformation.⁴²⁸ Manganese deficiency has also been related to reduced insulin synthesis in animal research and may contribute to dysregulation of maternal insulin metabolism and glycemia.^{424,429} Maternal manganese concentrations increase during pregnancy compared to nonpregnant women, which may mirror the upregulated fetal requirement.⁴³⁰ However, manganese may confer adverse health outcomes when exposure is both deficient and excessive during gestation. In epidemiological studies, both low and excess maternal concentrations of manganese have been associated with impairments to fetal growth and adverse neurodevelopmental effects in offspring.^{431,432} A recent study found that infant birth size was positively associated with maternal blood manganese and negatively associated with umbilical cord blood manganese, though this study did not examine non-linear models of association.⁴³³ Importantly, the findings of another recent cross-sectional study noted an inverted U-shaped association between maternal manganese concentrations and birth weight in infants.⁴³¹ With respect to maternal health, studies suggest that maternal manganese levels in pregnancy may be linked to lower risk for preeclampsia.^{434,435} A recent study which used data from the Boston Birth Cohort demonstrated that manganese was protective for child systolic blood pressure, which was stronger among mothers with higher levels of the heavy metal cadmium.³⁸⁹ The inclusion of manganese in prenatal supplements may confer protection to the mother and developing fetus during pregnancy and protect from later blood pressure increases particularly in children whose mothers were exposed to high levels of heavy metals in gestation. It is important to note the UL of manganese in adults, including women in perinatal periods, is 11 mg/day and intake at this level is quite unlikely to confer adverse effects.^{290,436}

While manganese concentrations increase during pregnancy, both deficiency and excessive levels can have adverse effects on fetal growth and neurodevelopment. Maintaining optimal manganese levels, through prenatal supplementation, may benefit maternal health by lowering the risk of conditions like preeclampsia and support child systolic blood pressure regulation, especially when mothers have been exposed to heavy metals during gestation.

The established UL for manganese is 11 mg/day, and there's minimal risk of adverse effects when intake is within this range.

Chromium

Trivalent chromium has been implicated as a regulator of glucose metabolism and insulin action.²⁹⁰ Indeed, a recent analysis of NHANES data from 1999-2010 suggested that individuals consuming chromium-containing supplements demonstrated a lower odds of having Type 2 Diabetes.⁴³⁷ Additionally, a recent systematic review and meta-analysis concluded that chromium supplementation may reduce HbA1c in individuals with Type 2 Diabetes.⁴³⁸ During gestation, lower levels of chromium have been observed among pregnant women with GDM compared to apparently healthy pregnant women.⁴³⁹ This reduction has also been demonstrated in tandem with elevations in heavy metals, such as cadmium and lead. Thus, environmental factors and heavy metal exposure may be related to the development of GDM.⁴³⁹ Murine studies have demonstrated that even with comparable energy intake, low dietary chromium intake is associated with increased body weight in female mice offspring.⁴⁴⁰ A follow up study noted that murine maternal diets with restricted chromium led to glucose intolerance in male offspring via modulations in DNA methylation linked to murine liver insulin signaling pathways.⁴⁴¹ Interestingly, a recent study found that 200 mcg/day of chromium supplementation in women with polycystic ovary syndrome who were considered candidates for in vitro fertilization conferred significant improvements to serum inflammatory mediators and gene expression of glucose transporter 1 (GLUT1), a glucose transporter protein involved in insulin signaling and glucose regulation.⁴⁴² Moreover, another study which examined 200 mcg/day chromium supplementation in a similar population of women with polycystic ovary syndrome noted that supplementation was associated with reduction in high-sensitivity c-reactive protein and a 16.7% increase in rate of pregnancy during the 8 week trial period, though this finding was not statistically significant.⁴⁴³ Further, supplementation and consumption of trivalent chromium is not linked to adverse effects and there is no UL established for chromium.²⁹⁰ The distinction of trivalent chromium is pivotal, as trivalent chromium is a trace element which occurs naturally in food, while hexavalent chromium in the environment is a toxic product resulting from various manufacturing processes.²⁹⁰

Trivalent chromium plays a crucial role in regulating glucose metabolism and insulin action, and studies suggest that chromium-containing supplements may lower the risk of Type 2 Diabetes. During pregnancy, lower chromium levels have been observed in women with gestational diabetes, possibly due to environmental factors and heavy metal exposure. Chromium supplementation, around 200 mcg/day, has shown promise in improving insulin sensitivity, reducing inflammation, and potentially increasing pregnancy rates in women with conditions like polycystic ovary syndrome. Trivalent chromium is generally considered safe for supplementation during pregnancy, and there is no established upper intake limit.

Molybdenum

Studies suggest that various essential trace elements are implicated in glucose regulation. Indeed, low molybdenum concentrations in pregnancy have been associated with the risk for glucose dysregulation, with women already at risk for GDM identified as particularly sensitive.⁴¹⁹ In adults, grain products account for about 20% of molybdenum consumed from the diet.⁴⁴⁴ This is concerning given the increasing adoption of gluten-free diets even among those without gluten sensitivities or Celiac's disease.³⁹ Moreover, while population surveillance of molybdenum intake is limited, the 1988-1994 NHANES data suggest that molybdenum intakes from supplements averaged 24 mcg/day for women, though the RDA for pregnancy is set at 50 mcg/day.^{290,445} However, the dietary reference intake for pregnancy was estimated using the EAR set for non-pregnant women, with an added 16 kg to the reference weight, based on the median weight gain reported in 7,002 women with good pregnancy outcomes.^{290,446} Therefore, supplementation above the RDA is likely necessary to be replete, and as there may exist prevalent molybdenum insufficiency and high molybdenum intakes are considered safe as this trace element is rapidly excreted in urine.^{290,447} Moreover, the established ULs for molybdenum are based on levels associated with compromised reproduction and fetal development in animal studies, and are set according to age between 1700-2000 mcg/day.²⁹⁰ This nutrient is rarely assessed and largely absent from most prenatal supplement formulations, shining a light on the potential for insufficiency in pregnant and lactating women.

Low molybdenum concentrations in pregnancy are associated with an increased risk of glucose dysregulation, particularly in women already at risk for gestational diabetes. Additionally, there is concern about the growing popularity of gluten-free diets, as grain products are a significant source of molybdenum. Supplementing above the RDA of 50 mcg/day is likely necessary for pregnant women to meet their molybdenum needs safely, as higher intakes have not

shown adverse effects. Additionally, molybdenum is often overlooked in prenatal supplements, highlighting the potential for insufficiency during pregnancy and lactation.

Need for more robust testing of perinatal nutrition and health status with respect to pregnancy-specific biomarkers and reference ranges.

There is overwhelming literature to support that nutritional deficits are causally linked to adverse outcomes for both the mother and offspring. Therefore, it is imperative that periconceptional nutritional status be evaluated with specific intent to support maternal and child health. Nutrient biomarker or metabolite concentrations provide objective data and are indicative of nutritional intake, bioavailability, and status.⁴⁴⁸ This data can be particularly powerful and have clinical utility to detect inadequacies when paired with nutrient intake data, especially given the bias associated with self-reported intakes.^{449,450} However, the assessment and interpretation of nutritional biomarkers is not straightforward, given the varied sensitivity of methods used to assess such indicators and the lack of consistency and accuracy of assays used for such quantitation.⁴⁵¹ Moreover, nutritional status biomarkers are affected by interactions among dietary intake, multiple pregnancies, acute or chronic inflammation, environmental exposures, obesity, genetic factors, and life stage-related physiological shifts among other factors.⁴⁵²⁻⁴⁵⁶

Therefore, to utilize nutrient-related biomarkers to detect nutrient status, such biomarkers must be at the least harmonized and assessed accurately with cut-offs that reflect population and subgroup specific exposures and physiology. Given the vast biological shifts which occur in pregnancy to support the mother and developing fetus, it is clear that the determination of valid and reliable biomarkers of nutritional exposure and the coordinated effort to define pregnancy-specific reference ranges are vital yet challenging issues.⁴⁴⁸ It is no surprise that pregnancy has been touted as a “biological confounder” in the interpretation of biomarkers which reflect nutrient status.⁴⁵⁷ However, it is time to shift the approach from the identification of deficiency to the identification of biomarkers and reference ranges which are determined to reflect optimized health indications specific to maternal and fetal health during and beyond pregnancy. With this, there exists mounting literature to support evidence-based shifts in many currently utilized biomarkers and reference cut-offs in relation to optimized maternal and offspring outcomes. Moreover, attention must be paid to the interplay, synergy, transport, signaling and assimilation among nutrients which support the optimal function of vast metabolic pathways.⁴⁵⁸ In this manner, nutritional assessments must be comprehensive and interpreted by a nutrition professional. Such assessments must be performed in tandem with robust health screening along with the integration of precision health metrics in perinatal periods to create a holistic individualized picture of needs during this sensitive window for shaping lifelong health resilience. Though it must be recognized that the power of this assessment approach cannot be actualized without expert care and support which considers the maternal voice, intuition, and experience.

Thus, perinatal assessments, support, and interventions must be attuned to the diverse network of interactions which influence nutritional status and response to interventions and be applied in a continuum, such that early assessment and intervention play critical roles in optimizing lifelong health resilience. In this sense, “early” is contextualized in both the sense of the overall lifespan as well as in sensitive gestational and postnatal windows which require particular evidence-based support. This action-orientated, integrated, and evidence-based care is a critical step in radically improving transgenerational health and paves a path forward for prevention and therapy which transcends perinatal health.

The utilization of nutrient biomarkers is essential for assessing periconceptional nutritional status, given their objectivity and ability to provide insights into nutritional intake and status. However, the assessment and interpretation of these biomarkers can be complex due to various factors, including interactions with dietary intake, inflammation, genetics, and physiological changes during pregnancy. To optimize maternal and offspring health, there is a need to establish valid and reliable biomarkers and reference ranges specific to pregnancy, focusing on holistic, individualized assessments, early interventions, and integrated, evidence-based care for lifelong health resilience and transgenerational health improvement.

Considerations for perinatal health and nutrition assessments

Beyond the scope of what will be thoroughly discussed in this paper, the Needed approach stands with the integration of standardized and robust perinatal health assessments including routine laboratory testing in tandem with nutrition status

assessments. Screening for factors or conditions which impact maternal and fetal health, such as testing for rubella, Rh factor, human immunodeficiency virus, hepatitis, and sexually transmitted infections, are standard in prenatal care.⁴⁵⁹ However, though the lifelong effects of impaired nutritional status on maternal and offspring health are well recognized, standardized and comprehensive nutritional assessments are lacking in perinatal care settings.⁸² Further, it is imperative to acknowledge that as our understanding of the complexities of human health and disease continue to evolve, the notion of what is considered routine or standard testing must transform in kind, particularly during malleable windows (i.e., the first 2000 days) for shaping lifelong health. Thus, we recognize the growing emphasis on integration of genomics testing and emerging multiomics assessments and their contribution to the understanding of synergistic and cumulative effects of exposures and biological factors in high resolution, with an aim to enhance individualized care.⁴⁶⁰ This integration will power the realization of precision nutrition assessments and guide personalized interventions. Given the Needed emphasis on comprehensive nutritional care, we also maintain a view that this goal is ultimately realized through utilization of a care team which includes a nutrition professional.⁴⁶¹ Based on clinical insights from the work of Emily Rydbom CN, HN, CNP, perinatal assessments would also ideally also incorporate Nutrition-focused Physical Exams which arm the care team with crucial findings to support the identification of deficiencies in key nutrients for perinatal health. This model also incorporates counseling and support to establish lines of success from assessment through intervention. Though the importance of perinatal nutrition is recognized by health organizations and agencies, it must be highlighted that a lack of harmonized integration of nutritional assessments and care in standard clinical practice ostensibly diminishes the utility of this acknowledgment. Indeed, during pregnancy many women don't receive nutritional counseling let alone holistic assessments and personalized interventions guided by nutrition professionals.⁸² The recognition of importance and the growing evidence in support of shifts in perinatal nutrition must be met with systematic shifts in clinical care standards in kind.

In the following sections, we will discuss some key biomarker and indicator assessments which reflect the complexities of health and nutritional status assessments, particularly in pregnancy, and highlight evidence related to perinatal specific reference ranges or cut-offs which may differ from non-pregnant values and aim to reflect maternal and offspring health outcomes. As research in this area is ongoing and incomplete, this section will serve as exemplary rather than comprehensive. With this in mind, a touchstone of the Needed approach is the emphasis on continued investigation in the areas of identification of nutritional status biomarkers and recalibration of perinatal reference ranges. Further, the Needed approach is progressive and in direct opposition to the historically stagnant approach to women's health and research. Thus, as the wheels of health research continue to turn, Needed will continue to evolve and has formulated its supplemental strategy to overcome many of the presently known environmental exposures, lifestyle practices, and genetic factors which may impact nutrient status and utilization with intentional consideration for the safe provision to diverse women. As such, beyond developing a robust understanding of perinatal nutritional status, we are poised to investigate the use of our meticulously designed supplements to assess their effects on nutrient status as well as maternal and offspring health outcomes. All of this in the effort to ultimately optimize health outcomes, rather than narrowly escape consequences of deficiency.

Standard and harmonized nutritional assessments and interventions are lacking in routine perinatal practice and demand integration to support maternal and offspring health. Also, there is emerging impetus to incorporate multiomics and systems-based approaches to generate personalized interventions which reflect complex biological and environmental interactions with respect to an individual's health and nutritional status. However, interdisciplinary care frameworks which incorporate a nutrition professional to translate findings from nutritional assessments into personalized interventions and support are a crucial step in shifting the current nutritional care paradigm.

Macronutrient assessment: Emphasis on health indications for interpretation by care team professionals

Lipid Screening: Dyslipidemia and Omega-3 Fatty Acid Status

Recent evidence suggests that less than 50% of women of reproductive age have had a lipid assessment, although national screening guidance supports lipid profile assessments in young adults.⁴⁶² Importantly, dyslipidemia is indicative of cardiometabolic dysfunction, a risk factor for cardiovascular disease, which remains the leading cause of mortality among women in the US.⁴⁶³ This is alarming, as early diagnosis remains a powerful tool for intervention and treatment initiation.^{462,464} Moreover, it has been found that among pregnant women, racial/ethnic disparities are present in lipid

screening.⁴⁶⁵ Recently, it has been asserted that early pregnancy may be a critical time to assess lipid parameters.⁴⁶² While plasma low-density lipoprotein cholesterol (LDL) and triglyceride levels increase over the course of pregnancy, from between 25-50% and 150-300%, respectively, the most profound increases in circulating lipids occur in the third trimester.^{466,467} Thus, early assessment of circulating lipids will provide key information and reflect pre-pregnancy lipid status and may provide insight into the magnitude of hyperlipidemia experienced in later pregnancy. Importantly, biological alterations in metabolism of lipids occur in pregnancy to support the developing fetus. However, disruptions in maternal lipid metabolism have been associated with increased risk of adverse pregnancy outcomes, including GDM, preeclampsia, and preterm birth.⁴⁶⁸⁻⁴⁷⁰ A recent study which examined the feasibility of early lipid screening in pregnancy found acceptance by obstetricians was high and 26% of patients presented with evidence of dyslipidemia.⁴⁶⁴ This highlights the importance of lipid screening throughout the perinatal period with particular emphasis on inclusion in early pregnancy.

The importance of adequate perinatal omega-3 PUFA intake from dietary sources or supplements, as well as the risks associated with inadequate intake have been discussed earlier in this paper. However, it is essential to note that as extensive evidence is available to support recommendations for omega-3s intakes in pregnancy, clinical assessment of omega-3 status will also provide valuable information in addressing personalized recommendations.⁴⁷¹ Several methods have been utilized to assess perinatal omega-3, and particularly DHA, status in research and clinical practice. Studies of pregnancy have reported RBC phospholipid DHA, plasma DHA, and whole blood spot DHA as markers of DHA status.^{116,472} A recent study examining low (200 mg) versus higher (1000 mg) dose supplementation of DHA to reduce early preterm birth found that those with low DHA status, defined as <6% RBC phospholipid DHA, assigned to the high dose group had half the rate of early preterm birth, compared to low dose.^{116,471,473} The authors noted that although DHA status will likely be correlated among methods, the percent DHA of total fatty acids will be greatest in RBC phospholipids. As such, omega-3 PUFA assessments in perinatal periods may provide critical information to women and care providers on nutritional needs. Further, a factor has also been posed to convert between whole blood spot DHA and RBC phospholipid DHA providing some comparability across methods of assessment.¹¹⁶

Early assessment of lipid parameters during pregnancy is essential, as dyslipidemia is indicative of cardiometabolic dysfunction, a significant risk factor for cardiovascular disease, which remains a leading cause of mortality among women in the US. Disparities exist in lipid screening among pregnant women, emphasizing the need for comprehensive and early assessment. In addition, assessing omega-3 polyunsaturated fatty acid status, particularly DHA, is crucial during pregnancy, as it plays a vital role in perinatal health, and various assessment methods are available to provide valuable insights for personalized recommendations.

Glycemic control: Emphasis on GDM

Among the physiological adaptations that occur to support pregnancy, modifications to glucose metabolism occur to maintain maternal status while promoting adequate provision of glucose to the fetus to support development.⁴⁷⁴ Early pregnancy is marked by reduced fasting glucose levels with stabilization in the second trimester, and subsequent decline in the third trimester.⁴⁷⁵ Decreases in maternal circulating glucose in early pregnancy are partially related to hemodilution and subsequent decline is related to upregulation in glucose utilization by the fetal-placental unit.⁴⁷⁶ Additionally, progressive elevations in circulating insulin are observed in gestation. Importantly, insulin plays a key role in regulating the gestational metabolic adaptations and maternal insulin sensitivity declines throughout pregnancy, which likely contributes to postprandial glucose elevations exhibited in pregnancy compared to preconception.^{477,478} Diminished insulin sensitivity in pregnancy is also paralleled by increases in gluconeogenesis and modifications to pancreatic β -cell mass and insulin secretion.⁴⁷⁹ Recent preclinical evidence also suggests that during pregnancy pancreatic α -cells may enhance maternal insulin production from nearby β -cells via their production of glucagon-like peptide 1 (GLP-1).⁴⁷⁷

In the US, 1 in 10 individuals have diabetes with Type 2 Diabetes representing nearly 95% of those cases.⁴⁸⁰ The overall rise in prevalence of obesity and type 2 diabetes has also been felt in the increase in prevalence of type 2 diabetes in women of reproductive age.⁴⁸¹ Alarming, approximately 30% of women of childbearing age with diabetes are undiagnosed.⁴⁸² It is also critical to note that racial/ethnic differences exist in the risk for cardiometabolic disease, as well as the prevalence of undiagnosed diabetes; though the extensive research behind the etiology of such disparities is beyond the scope of this paper.⁴⁸³ Moreover, the prevalence of GDM, defined as diabetes diagnosed in the second or third trimester of pregnancy that was not detected as diabetes preconceptionally, is also on the rise and a risk factor for

maternal development of type 2 diabetes and lifelong offspring metabolic derangements.^{481,484,485}

It is therefore imperative that screening for diabetes be implemented preconceptionally. Early intervention prior to pregnancy in those with diabetes can improve parameters of glucose regulation, i.e., HbA1c, and reduce adverse maternal and perinatal outcomes including risk for preterm birth, birth defects, SGA infants, and perinatal mortality.⁴⁸⁶ In the absence of screening prior to conception, early screening before 15 weeks of pregnancy has been recommended, though criteria for detection of diabetes in early pregnancy is the same as for nonpregnant individuals.⁴⁸¹ The American Diabetes Association (ADA) has recommended the following reference ranges to screen for early abnormal glucose metabolism; fasting glucose of 110–125 mg/dL or A1C 5.9%–6.4%.⁴⁸¹ Importantly, an HbA1c between 5.7% and 6.4% noted in early pregnancy has been shown to indicate patients at risk for developing GDM.⁴⁸⁷

Interestingly, while screening for GDM is recommended between 24–28 weeks of pregnancy, there is no harmonized consensus regarding diagnosis of GDM. However, two approaches are generally recommended in practice, including the International Association of the Diabetes and Pregnancy Study Groups 1-step screening approach and the 2-step Carpenter-Coustan screening approach.^{481,488} The 1-step approach is characterized by a 75g 2-hour oral glucose tolerance test (OGTT) during a fasted screening visit. The 2-step method involves an initial non-fasting 50g 1-hour glucose load test, followed by a fasting 100g 3-hour OGTT for individuals who fail the initial screening.⁴⁸¹ The cut-off values also vary by approach. While diagnostic incidence has been shown to be higher with the 1-step approach, a recent RCT comparing both methods found that there were no significant differences between groups in the risks of any primary outcome including adverse perinatal or maternal outcomes.⁴⁸⁹ Additionally, for those with diagnosed GDM, the 1-step 75 g OGTT is recommended by the ADA at 4–12 weeks postpartum.⁴⁸¹ Taken together, while implementation of glucose screening in gestation and postpartum are critical, additional trials evaluating longer term outcomes are necessary and underway to determine a harmonized approach.

Pregnancy involves significant changes in glucose metabolism and insulin sensitivity. Preconception screening and early intervention for diabetes are essential, as undiagnosed diabetes among women of childbearing age is relatively common and addressing glucose regulation prior to pregnancy can improve maternal and perinatal outcomes. Harmonized approaches for gestational diabetes screening and diagnosis are needed, and ongoing trials aim to determine the most effective methods for long-term outcomes.

Nutrient biomarkers & associated markers of transport, signaling, and sufficiency

Folate

As with many nutrients, the indicators utilized to establish dietary reference intakes for pregnancy and lactation were not founded on pregnancy-specific outcomes. A main example is the alignment of folate intakes with RBC folate. RBC folate is a robust bioindicator of long-term folate status and tissue stores.⁴⁹⁰ As mentioned previously here, the lowering of NTD risk was not factored into the dietary reference intakes for women in the US.⁷⁷ Thus, the current RDA is lower than recommendations established by the USPSTF (400–800 mcg supplemental folic acid/day) which did consider reduction of NTD risk as the primary indicator in forming recommendations for women of childbearing age.¹⁶² Importantly, research has indicated that RBC folate concentrations of >400 ng/mL (906 nmol/L) are optimal to reduce the risk of NTDs in women of reproductive age.⁴⁹¹ Such recommendations have also been supported by the WHO guidelines.⁴⁹² Given the presence of the genetic alterations in folate utilization, particularly the 677C>T MTHFR polymorphism, which lead to reduced conversion of folic acid to biologically active folate and blunted methylation potential, the gaps between folic acid intake and optimal levels of RBC folate to support NTD risk reduction may be greater than currently recognized.⁴⁹³ As discussed earlier, it is evident that supplemental 5-methylfolate presents an advantage in supplementation to support RBC folate status which should be examined relative to pregnancy specific outcomes. Supplementary markers of folate status include the short-term and diet responsive indicator serum folate and the functional marker homocysteine, given the role of folate in the remethylation of homocysteine to methionine.⁴⁹⁴ However, it should be noted that the remethylation of homocysteine to methionine is catalyzed by methionine synthase which is dependent on vitamin B12 and reliant on other nutritional cofactors.⁴⁹⁵ Therefore, while homocysteine will be elevated in the presence of folate deficiency, its concentration may also be impacted by deficiencies in other one-carbon cycle nutrients as well as genetic, environmental, biological, and lifestyle factors.⁴⁹⁶ As such, folate status and its links to birth defects are products of intricate interactions between folate intake, nutrient interactions, genetic considerations, and environmental factors.⁴⁹⁴

Research indicates that optimal RBC folate concentrations exceeding 400 ng/mL (906 nmol/L) are required to effectively reduce the risk of NTDs, particularly in individuals with genetic variations affecting folate utilization. Folate status and its relationship to birth defects are influenced by complex interactions involving folate intake, nutrient interplay, genetic factors, and environmental influences. Supplementary markers of folate status include the short-term and diet responsive indicator serum folate and the functional marker homocysteine, given the role of folate in the remethylation of homocysteine to methionine.

Vitamin B12

Vitamin B12 deficiency is largely defined in population research as a total serum B12 status of <148 pmol/L (200 ng/L).⁴⁹⁷ Recent evidence has also suggested that vitamin B12 deficiency may be present even when serum B12 falls within higher ranges of 125-250 pmol/L.³⁷ However, there exists a lack of harmonization related to cut-offs for serum B12 in perinatal periods as serum B12 does not represent direct utilization in metabolic reactions and is impacted by pregnancy associated biological shifts such as hemodilution and decreased production of haptocorrin.¹⁷⁸ Maternal concentrations of vitamin B12 decrease gradually over the course of pregnancy, and therefore evaluation of this biomarker in perinatal periods requires population-specific reference ranges in combination with direct and functional markers of vitamin B12 status.⁴⁹⁷⁻⁴⁹⁹ Holotranscobalamin (holoTC) is the active form of vitamin B12 and the portion of vitamin B12 available for fetal transport.⁴⁹⁹ Several studies have noted that holoTC concentrations remain stable throughout pregnancy and may serve as an additional indicator of B12 status.⁵⁰⁰ However, it is important to note that some studies have also reported declining concentrations of holoTC over the course of pregnancy and this marker may also require trimester-specific reference ranges.⁵⁰¹ Moreover, vitamin B12 is required as a cofactor for the conversion of methylmalonyl-CoA to succinyl-CoA by the enzyme methylmalonyl-CoA mutase to support energy production in the tricarboxylic acid cycle. Therefore, methylmalonic acid (MMA) has been further proposed as a functional biomarker of vitamin B12 status.⁵⁰² Levels of MMA have been shown to increase during pregnancy, though this may be related to increased fetal requirements or an impairment in vitamin B12 status.^{498,502-504} Further, studies have reported a negative correlation between holoTC and MMA during all trimesters of pregnancy.⁵⁰⁵ Importantly, a recent study found that women with lower holoTC concentrations measured at pre-conception had more pronounced elevations in MMA at week 32 of pregnancy which highlights the importance of evaluating and improving preconception B12 status.⁴⁹⁸

An analysis of an ethnically diverse cohort of pregnant women suggested that circulating levels of total B12 of <186 and <180 pmol/L and holoTC of <62.2 and <67.5 pmol/L in the first and second trimesters, respectively, reflected a higher likelihood of deteriorating B-12 status, regardless of ethnicity.⁴⁹⁹ The study findings also indicated that serum B-12 <89.9 and <84.0 pmol/L, holoTC <29.5 and <26.0 pmol/L and MMA >371 and >374 nmol/L, in the first and second trimesters, respectively, could reflect B-12 deficiency in pregnancy.⁴⁹⁹ Further, a recent analysis of a prospective cohort study of 434 mother-infant pairs found that maternal vitamin B12 concentrations of 312 to 408 pg/mL (230 -301 pmol/L) in the first trimester were associated with improvements in infant motor, language, and cognitive outcomes compared to maternal B12 levels <312 pg/mL (203 pmol/L) at 40 days postpartum.¹⁸⁹ Therefore, it is likely beneficial to achieve higher serum B12 levels during pregnancy, via modifications to dietary intake or supplementation, and to consider functional markers of vitamin B12 status recognizing that holoTC is a seemingly stable and robust indicator of B12 status by trimester.⁴⁹⁸

As maternal vitamin B12 concentrations gradually decrease during pregnancy, assessing vitamin B12 status in perinatal periods requires population-specific reference ranges and the consideration of direct and functional markers, such as holotranscobalamin and methylmalonic acid. Achieving higher serum B12 levels during pregnancy, through dietary changes or supplementation, is beneficial for maternal and infant health, as maternal B12 concentrations in the first trimester are associated with improved infant motor, language, and cognitive outcomes.

Vitamin B6

Vitamin B6, in its bioactive form of PLP, serves as a coenzyme in more than 160 metabolic reactions including those which support one-carbon metabolism and therefore cellular function, DNA synthesis, and neurotransmitter production.⁵⁰⁶ Therefore, circulating levels of PLP have been utilized as an indicator of vitamin B6 status. Plasma PLP levels decrease over the course of pregnancy and therefore, PLP levels in circulation differ substantially from preconception through postpartum periods.⁵⁰⁷ Reductions in PLP over the course of pregnancy may be attributed to confluence of factors including inadequate vitamin B6 intake, hemodilution, and increased transfer of PLP to the fetus.^{508,509} A recent study suggested that plasma PLP concentrations < 30 nmol/L at week 28 of pregnancy were associated with lower maternal PLP

levels throughout pregnancy and postpartum and in infants when assessed at 6 months.⁵⁰⁷ Such decreases below 30 nmol/L in PLP were also associated with elevations in the HKr index suggesting inadequate B6 status to support metabolic requirements. The HKr index is calculated as 3-hydroxykynurenine and divided by the sum of kynurenic acid + anthranilic acid + xanthurenic acid + hydroxyanthranilic acid and is considered a functional marker of vitamin B6 status as a metric of bioactive B6 in the kynurenine pathway.^{507,510} This study's findings suggest that plasma concentrations of >30 nmol/L in mid-late pregnancy may be required to support vitamin B6 bioactivity during pregnancy and lactation.⁵⁰⁷ Another longitudinal study of pregnant women who were not supplemented, demonstrated decreased levels of plasma PLP during pregnancy from 36.2 nmol/L to 16.8 nmol/L with concomitant increases in cystathionine, which is also considered as a functional marker of vitamin B6 status reflecting the requirements for vitamin B6 as a coenzyme in the transsulfuration pathway.⁵¹¹ In this study, PLP concentrations were reduced by about 50% throughout pregnancy.⁵¹¹ However, while this study did not note a correlation between maternal vitamin B6 intake and PLP concentrations during pregnancy, it is important to note these individuals did not receive supplementation. Additionally, it is important to consider the role of riboflavin, as a coenzyme in the formation of PLP, and therefore riboflavin status in the assessment of vitamin B6.²¹⁴

During pregnancy, plasma PLP levels decline due to factors such as inadequate intake, hemodilution, and increased transfer to the fetus. Research suggests that maintaining plasma PLP concentrations above 30 nmol/L during mid-late pregnancy is necessary to support vitamin B6 bioactivity, and this level is associated with better metabolic outcomes during pregnancy and lactation.

Vitamin D

As discussed earlier, though important to reiterate in the context of nutritional assessment, it has been shown that a treatment target for vitamin D, set to a level of 25(OH)D >50 nmol/L (20 ng/mL) or even >75 nmol/L is too low regarding optimized health outcomes particularly in pregnancy.²⁸¹ Recent studies have found that when 25(OH)D levels are raised to 40 ng/mL, a greater attenuation of adverse pregnancy outcomes across diverse racial and ethnic groups is noted.^{266,512} This level of circulating 25(OH)D during pregnancy has also been associated with normalized calcium homeostasis and vitamin D metabolism, such that conversion of 25(OH)D to 1,25 dihydroxyvitamin D (1,25[OH]2D) is optimized.²⁸⁰ In a study of pregnant women aged 18-45, maternal 25(OH)D concentrations \geq 40 ng/mL were associated with a significant reduction in preterm birth risk of 62%, with similar reductions in preterm birth risk noted by race/ethnicity.⁵¹² A recent review of the evidence related to vitamin D supplementation during pregnancy and birth outcomes also suggested that pregnant women would benefit from achieving a circulating vitamin D >40 ng/mL to improve birth outcomes including primary cesarean section and comorbidities of pregnancy.²⁸¹

The current vitamin D treatment target for pregnancy, set at a 25(OH)D level of >50 nmol/L (20 ng/mL), is considered too low for optimizing health outcomes during pregnancy. Recent studies indicate that raising 25(OH)D levels to 40 ng/mL is associated with a greater reduction in adverse pregnancy outcomes across various racial and ethnic groups, as well as normalized calcium homeostasis and vitamin D metabolism. This emphasizes the importance of aiming for higher vitamin D levels during pregnancy to improve birth outcomes.

Calcium

Total serum hypocalcemia during pregnancy has been associated with adverse outcomes such as preeclampsia and low birth weight, though study findings have been equivocal.⁵¹³⁻⁵¹⁷ However, nearly half of circulating calcium is free ionized calcium, representing the form which is metabolically active, and the remaining calcium is bound to plasma proteins and anions.⁵¹⁸ During pregnancy, total calcium levels decrease as a result of hemodilution and the fall in circulating albumin, though ionized calcium levels remain stable.⁵¹⁹ Therefore, ionized calcium is a key indicator to determine calcium status in pregnancy. There is evidence to suggest that maternal ionized calcium <1.31 mmol/L is associated with significantly greater odds for low birth weight, low birth length, and maternal hypertension during pregnancy.⁵¹⁸ A recent case-control study also found that women with preeclampsia had lower levels of ionized calcium level (1.1 mmol/L \pm 0.11) and total total serum calcium level (1.99 mmol/L \pm 0.35) compared to controls.⁵¹⁵ This study also noted that the normotensive women tended to fall within reference ranges of 2.1-2.55 mmol/L for serum calcium and 1.16-1.32 mmol/L for ionized calcium whereas those with preeclampsia fell below these ranges.⁵¹⁵

During pregnancy, total calcium levels decrease due to hemodilution and changes in albumin levels, but ionized calcium levels remain stable and are a critical indicator of calcium status in pregnancy. Low ionized calcium levels (less than

1.31 mmol/L) have been associated with increased odds of low birth weight, low birth length, and maternal hypertension.

Zinc

Plasma or serum zinc concentrations are utilized as biomarkers of zinc status, especially at the population level of assessment as circulating zinc responds, yet heterogeneously, to fortification and supplementation interventions.^{520–522} Importantly, only 1% of whole body zinc is present in circulation and plasma zinc concentrations are also impacted by other factors such as sex and pregnancy which must be considered in assessments.⁵²² Additionally, pregnancy associated physiological changes, such as hormonal fluctuations and plasma volume expansion, may impact the relationship between dietary zinc intake and plasma zinc levels.^{522,523} As such, zinc needs increase during pregnancy though circulating concentrations decline.⁵²³ Recent studies have suggested cut-offs for assessing zinc deficiency in females ages 10 and older using serum zinc values ranging from <66 mcg/dL to <70 mcg/dL depending on morning fasting status.⁵²² Though women are more likely to fall below this cutoff, findings from NHANES II reported zinc concentrations of 69.8 mcg/dL in pregnancy.⁵²⁴ Lower cut-offs to suggest deficiency have been suggested for women in early (56 mcg/dL) and mid-late (50 mcg/dL) pregnancy, however a significant decline in circulating zinc levels <60 mcg/dL has been associated with a greater risk of low birth weight infants.^{524–526} An emerging biomarker, metallothionein has also been proposed to assess zinc status. This protein assists with transit of zinc through erythrocytes once absorbed and its expression is regulated by metal-responsive transcription factor 1 (MTF-1) which is highly sensitive to zinc levels in the cell.⁵²⁷ Studies have also demonstrated that metallothionein expression is upregulated with zinc supplementation, though more studies to examine its utility in population studies are needed.⁵²⁸ Zinc status assessments may also be complemented by dietary assessments and assessments of location specific food composition databases which can provide evidence of zinc bioavailability based on food matrices and phytate-to-zinc ratios.⁵²² It is important to note that zinc absorption in the gastrointestinal tract is impacted by nutrient interactions, such as competition for absorption with copper and iron and the formation of complexes consisting of calcium, zinc, and phytates which cannot be absorbed.^{522,529–531}

Iron

The maintenance of iron status is tightly regulated in a manner which avoids toxicity through modifications to iron absorption, regulation of iron stores, and iron reprocessing from cells at the end of their life spans.⁵³² Iron requirements increase during pregnancy, and fetal accretion of iron will occur at the expense of maternal iron.⁵³³ Therefore, it is vital to ensure iron intake is meeting increased demands to optimize processes which regulate maternal systemic and cellular iron homeostasis and support fetal transport and requirements.⁵³² It is also critical to assess maternal iron status in preconception and early pregnancy, as preclinical research has demonstrated that correcting maternal iron deficiencies experienced in early pregnancy may only partially attenuate deficiency-associated adverse effects to fetal development.⁵³⁴ The assessment of iron status biomarkers during pregnancy is complicated by trimester-specific fluctuations to the amount of body iron and the distribution of body iron. As such, while in the early first trimester iron requirements may decrease slightly with decreased iron absorption, notable increases in placental and fetal growth and plasma volume expansion occur late in the first trimester with iron needs increasing most during the second half of pregnancy.⁵³² Notably, pregnancy is considered an inflammatory state and inflammatory processes may impact the interpretation of certain iron status biomarkers.⁴⁵³ However, with all of this said there exists a lack of harmonized standards for iron status assessment throughout gestation.⁵³⁵ Thus, iron deficiency may often be unidentified in women during pregnancy. Moreover, current guidance often only encourages testing of iron stores, i.e., serum ferritin, when hemoglobin measures are low.^{535–537} This is concerning, as iron deficiency is the most prevalent cause of anemia, yet iron stores are depleted before erythropoiesis is compromised.^{535,538}

In the first trimester of pregnancy, hemoglobin concentrations begin to decline, thus the threshold for anemia is decreased to 110 g/L based on guidance from the CDC and WHO.^{539,540} Though a continued decline noted in the second trimester resulted in an even lower threshold for anemia by the CDC of 105 g/L for this trimester only.⁵³⁹ While iron requirements increase in mid and late pregnancy, it should be noted that hemoglobin concentrations begin to rise in the third trimester in women who supplement with iron throughout gestation.⁵⁴¹ However, reliance on hemoglobin alone is not adequate to diagnose iron deficiency in pregnancy, particularly in early stages of deficiency and due to other nutritional deficits and conditions which cause anemia.³⁴⁶ Thus iron-specific biomarkers, including serum ferritin and hepcidin, may better discern iron-deficiency from other causes of anemia.³⁴⁶ Hepcidin is a negative regulator of iron absorption and distribution, and this biomarker declines throughout pregnancy, providing support for increased iron needs during gestation.⁵⁴² There is also growing interest in the utility of hepcidin as an iron status biomarker during pregnancy, though

more research is needed.⁵⁴³ A recent systematic review which examined guidelines for identification of iron deficiency, concluded that a cutoff for serum ferritin of 100 mcg/L should be utilized to define iron deficiency in most conditions.⁵⁴⁴ However, it should be noted that serum ferritin, a robust biomarker of the body's storage iron capacity, declines in early pregnancy and continues to decline throughout pregnancy if not supplemented.⁵³² Moreover, a cutoff for females of <15 mcg/L has been accepted by the WHO as suggestive of iron depletion in the first trimester of pregnancy.⁵⁴⁵ Though it should be noted that other organizations, such as the British Columbia Ministry of Health, support higher thresholds of <30 mcg/L to indicate deficiency which is likely more sensitive to diagnosing deficiency.⁵⁴⁶ It must also be considered that ferritin is an acute phase reactant and sensitive to rise in the presence of systemic inflammation. Other studies have suggested that a serum ferritin concentration of <70 mcg/L in early pregnancy identifies a need for iron prophylaxis, with supplemental dose requirements increasing inversely with serum ferritin concentrations.³⁵⁴

Iron status assessments during pregnancy are complicated due to trimester-specific fluctuations in body iron levels, but relying solely on hemoglobin levels to diagnose iron deficiency is inadequate, especially in the early stages. Iron-specific biomarkers, including serum ferritin and hepcidin, may better discern iron-deficiency from other causes of anemia. A cutoff for serum ferritin of 100 mcg/L has been suggested to define iron deficiency in most conditions. However, it should be noted that serum ferritin declines throughout pregnancy if not supplemented, and supplemental doses should likely increase inversely with serum ferritin concentrations.

Iodine

Iodine status is critical for thyroid hormone production and metabolism and thereby maternal iodine status is vital for fetal growth and development.⁵⁴⁷ Moreover, placental transport of thyroid hormone to the fetus during the first trimester of pregnancy is essential as the fetus develops its own thyroid for hormonal production.⁵⁴⁸ Iodine deficiency during pregnancy can result in severe adverse outcomes including neonatal hypothyroidism, stunted growth, infant mortality, and congenital defects.^{549,550} Urinary iodine concentration (UIC) is utilized to assess iron status in the population though its utility is limited to predict individual status.⁵⁵¹ Nevertheless, studies have demonstrated that serum iodine concentration (SIC) is associated with UIC and thyroid function in pregnant women.⁵⁵² A recent study of pregnant women noted a higher risk for hypothyroxinemia in women with a SIC of <79.9 mcg/L, yet those with an SIC >138.5 mcg/L had a greater risk for thyrotoxicosis.⁵⁵² Thus, SIC within these ranges may be supportive of an optimized iodine status in pregnancy. Additional markers have been posed to assess iodine status and thyroid function for a more comprehensive picture of iodine nutriture and health status, including TSH, T4, T3 and thyroglobulin.⁵⁴⁸ Thyroglobulin, a structural protein in which T3 and T4 are synthesized, is correlated with the level of iodine deficiency and touted as a more sensitive marker of iodine status than other thyroid hormones.^{553,554} Moreover, a recent meta-analysis found that with respect to pregnancy, thyroglobulin concentrations may be a sensitive marker of iodine deficiency in pregnant women with median UIC <100 mcg/L.⁵⁵⁴

While urinary iodine concentration (UIC) is commonly used to assess population-level iodine status, serum iodine concentration (SIC) has been associated with thyroid function in pregnant women. Maintaining SIC within certain optimal ranges may support an optimized iodine status during pregnancy. Additionally, markers like thyroglobulin have been proposed to provide a more comprehensive picture of iodine status, with thyroglobulin being considered a sensitive marker for iodine deficiency in pregnant women with median UIC <100 mcg/L.

Considerations for Other Essential Trace Minerals

As previously reviewed here, essential trace minerals play key roles in maternal and fetal health, however there exists no consensus on optimized levels of several circulating trace elements during perinatal periods. While the assessment and interpretation of nutritional biomarkers in pregnancy is a challenge, evidence mounts to suggest that circulating nutrient biomarkers are associated with maternal and offspring health outcomes. Thus, continued research is necessary to assess and identify trace mineral status biomarkers in perinatal periods with respect to maternal and fetal health outcomes, and to account for confounding variables which may impact status and biomarker interpretation.

For example, selenium concentrations along with glutathione peroxidase activity decline throughout pregnancy.³⁸⁰ These declines have been associated with a diminished antioxidant status in pregnancy, and low serum selenium concentrations have been associated with recurrent pregnancy loss and preterm birth.^{385,555} Additionally, recent evidence suggests that serum selenium status and glutathione peroxidase enzymatic activity are reduced in women

low selenium concentrations had an increased relative risk for subfertility compared to those with higher circulating selenium levels.⁵⁵⁷

In regard to copper, circulating concentrations increase during pregnancy and begin a return to baseline following delivery.⁵⁵⁸ Importantly, studies which examine copper status in healthy pregnancies are lacking.⁵⁵⁹ However, evidence suggests that aberrant alterations to circulating copper may be associated with adverse health outcomes. For example, there is evidence to support that maternal serum copper and ceruloplasmin, the main copper-binding protein, are elevated in women with preeclampsia.^{417,560,561} Interestingly, low serum copper has also been associated with higher risk for developing pregnancy induced hypertension, though participant BMI impacted serum copper measures such that a higher BMI was associated with elevated serum copper levels.⁴¹⁵

Moreover, evidence suggests that higher maternal circulating concentrations of magnesium are linked to reductions in the incidence of GDM and preeclampsia, and lower circulating magnesium has been noted in women with GDM compared to pregnant women without GDM.^{393,400} It should be noted that although serum magnesium is commonly used in clinical status assessments, its utility is diminished given only 1% of body magnesium is present in circulation, with most existing intracellularly.⁵⁶² Additionally, bone stores of magnesium can be released to offset deviations in serum status.⁵⁶³ However, recent evidence suggests that serum magnesium levels <.82 mmol/L paired with urinary magnesium excretion of 40-80 mg/day is a robust indicator of magnesium deficiency.⁵⁶⁴

Optimal circulating levels of essential trace minerals during pregnancy are still a subject of ongoing research. However, there is growing evidence that these trace minerals are associated with maternal and fetal health outcomes.

Selenium concentrations and glutathione peroxidase activity decline during pregnancy which have been linked to diminished antioxidant status, recurrent pregnancy loss, and preterm birth. Additionally, studies have shown that women with low selenium concentrations have an increased relative risk for subfertility.

Evidence suggests that aberrant alterations to circulating copper and ceruloplasmin, the main copper-binding protein, may be associated with adverse health outcomes in pregnancy such as preeclampsia.

Magnesium levels in circulation appear to have associations with pregnancy-related conditions such as gestational diabetes and preeclampsia. Recent evidence suggests that serum magnesium levels <.82 mmol/L paired with urinary magnesium excretion of 40-80 mg/day is a robust indicator of magnesium deficiency.

Need for additional considerations beyond typical macro and micronutrient supplementation

Plant-derived nutrients

Macular Pigment Carotenoids

The xanthophyll carotenoids lutein (L) and zeaxanthin (Z) have been recognized for their roles in preventing the loss of vision associated with age-related macular degeneration (AMD) and enhancing optical and cognitive performance.⁵⁶⁵ The attention to these plant-derived nutrients has increased since the publication of the Age-Related Eye Disease Study 2 (AREDS2) study analyses which set the standard for L and Z use in individuals with intermediate or advanced AMD.⁵⁶⁶ L and Z accumulate in the retina, particularly the macula lutea, where they are components of the macular pigment and are essential for vision.⁵⁶⁷ Further, studies have shown that these carotenoids accumulate in the fetal eye and neural tissues, particularly in later pregnancy, suggesting that maternal status may influence fetal eye and brain development.^{568,569} The placental transfer of nutrients which occurs during the third trimester of pregnancy may also contribute to low maternal stores of L and Z in the perinatal period.⁵⁷⁰ However, these plant-derived nutrients must be obtained through diet or supplementation, though typical consumption in the US is estimated to be 1-2 mg/day and 0.2-0.4 mg of L and Z, respectively.⁵⁷¹ Therefore, the addition of L and Z to the nutrient profile of perinatal supplements may serve to benefit the cognitive and visual health of the mother and fetus. The initial findings recently published from the Lutein and Zeaxanthin in Pregnancy (L-ZIP) trial found that the addition of 10 mg L and 2 mg Z per day to the standard-of-care prenatal supplement in the first trimester enhanced maternal carotenoid status as well as infant cord blood and skin carotenoids, compared to the standard-of-care control.⁵⁷²

This study also found a significant association between maternal and infant systemic carotenoid status postpartum.⁵⁷² Importantly, this study found a dose similar to the AREDS2 formula was safe and well tolerated in pregnancy and L and Z are generally recognized as safe by the FDA. Though reports from this trial are still forthcoming, a recent abstract from this trial reported a 20% increase in macular pigment in infants whose mothers were in the treatment group, compared to the standard-of-care control.⁵⁷³ Thus, as evidence accumulates in support of these particular carotenoids in adult and fetal health outcomes, the safe addition of L and Z into a perinatal dietary supplement strategy should be emphasized

The xanthophyll carotenoids lutein and zeaxanthin are essential for vision and cognitive performance, with their supplementation during pregnancy showing potential benefits in enhancing maternal and fetal carotenoid status. As evidence accumulates in support of these particular carotenoids in adult and fetal health outcomes, the safe addition of lutein and zeaxanthin into a perinatal dietary supplement strategy should be emphasized.

Prebiotics and Probiotics

There is evidence to suggest that along with the profound biological changes undergone during pregnancy, significant modulations to the microbiome occur during this timeframe.⁵⁷⁴ Moreover, microbial composition shifts occur at various sites during pregnancy, such as the gut, vagina, and oral cavity, which influence the function of physiological systems.⁵⁷⁵ In a recent study of pregnant women, progression from the first to third trimesters was marked by an increase in the relative abundances of Proteobacteria and Actinobacteria, with a diminished overall bacterial diversity.⁵⁷⁴ While some of these fluctuations have been surmised as advantageous to support normal pregnancy, similar modifications to intestinal flora may confer metabolic dysregulation in non-pregnant individuals.⁵⁷⁴ Importantly, such microbial alterations in non-pregnant individuals have been linked to obesogenic exposures.⁵⁷⁶ Thus, dysbiosis is prompted in part by obesogenic dietary patterns and promotes both metabolic endotoxemia and chronic low-grade systemic inflammation, augmenting the risk for chronic disease development.^{577,578} It is therefore probable that pre-pregnancy dysbiosis is widespread and may lead to the development of complications for the pregnant mother and the transmission of altered gut microbes to the offspring. This scenario can have a profound negative impact on the lifelong health and resilience capacity of both the mother and offspring.

Thus, it is unsurprising that conditions such as mode of delivery and infant feeding practices have been linked to the development of the infant gut microbiome and concerning that infant dysbiosis has been associated with augmented risk for adverse health outcomes including gastrointestinal disease, metabolic disease, immune-mediated disease, and asthma.⁵⁷⁹⁻⁵⁸³ Indeed, it has been shown that the transmission of microbes from mother to offspring via several routes contributes substantially to the seeding and colonization, and thus the development, of the infant microbiome.¹⁴⁵ Moreover, it has been noted that maternally transmitted bacterial strains have a higher probability of persisting in the infant gut.¹⁴⁵ Therefore, it is plausible that as maternal dysbiosis is associated with maternal metabolic dysregulation and chronic disease risk, such microbial imbalance can impact both maternal and infant health.⁵⁸⁴

A prime example is GDM, which is rising in prevalence and presents significant maternal and fetal health concerns.⁵⁸⁵ While it has been noted that in normal pregnancy maternal microbial composition shifts particularly in the third trimester, it has been demonstrated that the maternal gut microbiome is altered in GDM throughout pregnancy and postpartum.^{574,586-588} Dysbiosis of the gut microbiota may contribute to the development of inflammation and insulin resistance in GDM. Further, a recent study also showed that GDM can impact the neonatal microbiota at birth, and microbial variation trended similarly between mothers and infants suggesting an intergenerational persistence of GDM-associated microbial modulation.⁵⁸⁷ Moreover, research has demonstrated that infants born to mothers with GDM also demonstrate significantly diminished microbial diversity compared to those born to mothers without GDM.⁵⁸⁹ Importantly, infants born to mothers with GDM have higher odds of developing obesity at ages 9-11.⁵⁹⁰ The presence of dysbiosis has also been implicated as having a causative role in the development of other metabolic complications during pregnancy including preeclampsia.⁵⁹¹

Beyond the gut, hormonal fluctuations and physiological changes which occur during gestation can lead to shifts in the oral microbiome. These alterations can increase susceptibility to oral conditions, such as gingivitis and periodontal diseases, which are linked to adverse pregnancy outcomes, including low birth weight and preterm birth.⁵⁹² Studies have suggested these associations may arise from translocation of periodontal bacteria to the placenta and fetal circulation, or systemic circulation of endotoxins and inflammatory mediators which originate from the site of infection and may impact

fetal development and pregnancy maintenance through inflammatory processes.⁵⁹² As such, the oral microbiome plays a crucial role in maternal and neonatal health during pregnancy, underscoring the importance of comprehensive maternal oral care to reduce the transmission of harmful oral bacteria to the fetus and promote healthy outcomes during this critical period.

Additionally, the vaginal microbiome remains relatively underexplored, despite its significant impact on various aspects of women's health, including fertility, pregnancy outcomes, and susceptibility to infections.⁵⁹³ A balanced vaginal microbiome, characterized by a dominance of *Lactobacillus* species, is associated with a lower risk of complications, such as preterm birth, low birthweight, and miscarriage.^{593,594} On the other hand, disturbances in the vaginal microbiome, as seen in Bacterial Vaginosis, can lead to adverse reproductive health outcomes, including an increased risk of sexually transmitted infections, pelvic inflammatory disease, and preterm birth.⁵⁹³ While the currently approved antibiotic treatment options for bacterial vaginosis do alleviate the condition in an immediate sense, upwards of 50% of women will experience recurrence within 12 months of antibiotic treatment.⁵⁹⁴ Thus adjunctive options which recalibrate the vaginal microbiome may augment prevention and treatment strategies

Fortunately, there exist opportunities to shift the composition and thus functions of microbial inhabitants. The supplementation with pre and probiotics may confer advantageous modulations to the intestinal microbiota and therefore host health, supplying the intestinal mucosa with live beneficial microbes and fermentable substrates which stimulate enrichment and activity of certain microorganisms residing in the gastrointestinal tract associated with health benefits.^{595,596} There is extensive evidence to support the use of pre- and probiotics for the prevention or amelioration of conditions associated with dysbiosis including gastrointestinal diseases, respiratory infections, mood disorders, and cardiometabolic disease risk factors.⁵⁹⁵⁻⁵⁹⁹ In the case of probiotics, some mechanisms which confer health benefits are observed across taxonomic groups while other effects may be more strain specific.⁶⁰⁰ Thus, while a probiotic may exert several beneficial effects such as immunomodulation, nutrient synthesis, and intestinal barrier maintenance, single strains cannot be expected to confer all health-promoting benefits and a combination of evidence-based strains is likely to result in maximized effects.⁶⁰⁰

While a review of the evidence regarding specific probiotic strains and prebiotics is beyond the scope of this paper, emerging preclinical and clinical evidence is mounting support the use of pre- and probiotics in the perinatal period for maternal and offspring health outcomes given vertical and horizontal transmission of the maternal microbiome. It is also worth noting that *Bifidobacterium* and *Lactobacillus* are key well-studied genera contributing to a favorable microbiome.⁶⁰⁰ Maternal intake of pre- and probiotics may confer benefits to maternal cardiometabolic health, oral health, incidence of mastitis, prevention and treatment of bacterial vaginosis, and mental wellness, as well as augment infant health outcomes.⁶⁰¹⁻⁶⁰⁶ Preclinical evidence suggests that supplementation with prebiotics in obese murine pregnancy augments maternal glucose regulation and is protective against offspring weight gain.⁶⁰⁷ There is also promising evidence to suggest that perinatal probiotic treatment can improve glycemic control and prevent GDM.^{608,609} In the case of confirmed GDM, a recent Cochrane systematic review in meta-analysis reported that probiotic supplementation may improve cardiometabolic parameters, including Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and inflammatory and oxidative stress biomarkers, compared to a placebo or standard-of-care control.⁶¹⁰ As noted, *Lactobacillus* species are a crucial bacteria to a healthy vaginal microbiome and recent studies have found orally and vaginally delivered probiotics may restore and sustain balance to the vaginal microbiome and lower recurrence in women with bacterial vaginosis.^{611,612}

Additionally, murine studies have suggested that perinatal prebiotic supplementation results in improvements in offspring immune responsiveness and gut barrier function with reductions in the development of offspring food allergies.^{613,614} A body of preclinical findings also support that maternal probiotic treatment may improve intestinal barrier integrity and reduce intestinal inflammation in offspring.⁶¹⁵ A recent clinical trial found that prenatal supplementation with *Limosilactobacillus reuteri* LR92 resulted in reduced frequency and severity of colic in infants.⁶¹⁶ Maternal probiotic supplementation has also been shown to lower offspring incidence of eczema and atopic dermatitis.⁶⁰⁶ Furthermore, results of animal studies suggest that probiotic treatment can confer beneficial effects on anxiety-like and depressive-like behaviors.^{617,618} Moreover, preclinical evidence is available which posits that perinatal probiotic supplementation may reduce anxiety behaviors in offspring.⁶¹⁹ A recent study which evaluated the effects of *Lactobacillus rhamnosus* HN001 (HN001) treatment during pregnancy on postnatal symptoms of depression and anxiety, found that women HN001

supplemented women has significantly lower PPD and anxiety scores compared to controls.⁶⁰⁵ Importantly, a recent systematic review and meta-analysis reported that the use of prebiotics and probiotics during pregnancy are safe for use during perinatal periods.⁶²⁰

Pregnancy leads to significant alterations in the microbiome, with microbial changes occurring at various sites including the gut, vagina, and oral cavity. These changes can impact maternal health, fetal development, and the lifelong health of both mother and child. Pre- and probiotic supplementation during the perinatal period is considered safe and shows promise in supporting maternal cardiometabolic health, oral health, mental wellness, and the vaginal microbiome as well as augmenting infant health outcomes.

A critical signal to paternal nutrition and male health

Although accumulating evidence suggests the crucial role of maternal nutrition in connection to gestational and offspring outcomes, it is clear that paternal exposures also contribute to paternal health and fertility as well as offspring health.⁶²¹ While this literature demands its own comprehensive review, attention must be paid within the scope of this paper as it is a key chapter in the complete story regarding the essentiality of proper parental nutrition in periconceptional periods and throughout the lifespan. Factors such as aging and impaired nutritional intake can adversely influence sperm quality and motility and ultimately impact male fertility.^{622–624} Additionally, it has been demonstrated that sperm carry their own epigenome, which may influence male reproductive health and be delivered to the zygote ultimately impacting intergenerational health.⁶²⁵ Importantly, paternal exposures can promote epigenetic modifications, with paternal nutrition in pre-pubertal through adult timeframes emerging as a potent factor for regulation of the germ cell epigenome and male reproductive physiology.^{621, 626} Additionally, such paternal lifestyle factors may also ultimately modulate the maternal uterine environment, regulating offspring outcomes indirectly. Thus, the DOHaD is incomplete without the consideration of paternal exposures and the mediating role of paternal nutrition.⁶²⁷

Poor dietary patterns, such as obesogenic diets, have been associated with systemic inflammation and oxidative stress which can adversely impact sperm cell quality and function.⁶²⁸ Conversely, healthy dietary patterns rich in micronutrients and phytochemicals with bioactive properties have been shown to augment antioxidant defenses and mitigate inflammation with positive effects on male fertility.^{621,625} However, given the complexity of the current landscape of health and nutritional status, intentional supplemental support is often necessary. For example, studies have demonstrated that supplementation with antioxidants such as coenzyme Q10, an antioxidant which is produced endogenously and also consumed through diet, in patients with idiopathic infertility results in improvements in sperm motility, density, and morphology.^{629,630} Additionally, recent evidence suggests supplementation with omega 3 PUFAs, key components of sperm cell plasma membranes, can augment seminal antioxidant activity and improve sperm parameters.^{631, 632}

Moreover, as noted previously, paternal nutritional status may influence offspring outcomes via epigenetic regulation. In murine studies, deficiencies in one-carbon nutrients such as folate have been linked to offspring birth defects and altered sperm DNA methylation patterns in genes associated with development, chronic disease, and autism.⁶³³ These findings suggest a critical role of paternal one-carbon nutrition in offspring health outcomes. Another study exposed male rats to undernutrition, and noted detriments to fertility and sperm methylation, though supplementation with an antioxidant mixture including vitamin C, vitamin E, folate, trace minerals, and green tea extract mitigated oxidative damage to sperm DNA and prevented outcomes associated with metabolic dysregulation in offspring.⁶³⁴ Though more research is needed, it is evident that paternal nutrition and intentional nutrient support in sensitive windows are essential for fertility and play a critical role in the trajectories of intergenerational health outcomes.

Paternal exposures, including nutritional factors, can influence male fertility, sperm quality, and even impact the epigenome carried by sperm, potentially affecting the health of future generations. Optimized nutrient supplementation may favorably influence male fertility, with healthy diets and intentional provision of antioxidants and omega-3 fatty acids showing promise in improving sperm parameters. Furthermore, paternal nutritional status may influence offspring outcomes through epigenetic mechanisms, emphasizing the importance of paternal nutrition in the Developmental Origins of Health and Disease.

Needed Approach

A notable flaw in the current approach to perinatal nutrition is the isolated focus on prenatal periods, and a lack of regard for the continuum of women's health throughout several phases of life which interact to not only support a healthy gestation but intricately shape and scaffold the biological milieu for lifelong and intergenerational health. It is evident that a woman's perinatal and offspring health are hinged on a balance of lifelong nutrition and the intentional provision of nutrients during the narrow window of gestation.² Therefore, the historic and ongoing lack of attention to research and policy related to women's health is an inherent crisis for the future of human health and has broad implications for our health systems.⁶³⁵ Moreover, research methodologies which aim to investigate nutritional interventions in pregnancy must evolve to approach perinatal nutritional status in a holistic manner to target the intricacies and interactions among complex systems.

To address women's nutrition and health as a continuum is to employ a prominent and underappreciated opportunity to imbue in women a sense of control over adverse health outcomes which may seem inevitable in a modern environment. Nutrition is not the singular solution along this path, yet it is a powerful and necessary tool in the face of transgenerational and modern exposures. Not to mention, that this focus will allow a woman to enter the perinatal period with optimized nutritional status thereby contributing to a realized optimal milieu for fetal support and lifelong maternal and offspring outcomes. We must intervene now to create a future where the importance of women's health is not marginalized to mitigating deficiencies in periods which support fetal development and offspring outcomes but is reimagined to meet optimal needs throughout the lifespan to fortify a woman's lifelong health and thereby the health of future generations, communities, and societies at large.⁶ This shift in focus must be contextualized to optimize nutritional status in the overall lifespan as well as in sensitive gestational and postnatal windows which require individualized and evidence centered support. It is evident that the current approach to perinatal nutrition is unsustainable. Such sensitive periods for maternal and offspring outcomes are heavily susceptible to the translational lag in evidence which supports the unequivocal need for comprehensive and personalized perinatal nutritional support and additional research to glean the true definition of optimized nutrition for diverse women. The consequences are manifest in the present landscape of perinatal health.

We can look to unprecedented rates of infertility, neurocognitive deficits, chronic disease, adverse mental health outcomes among many others to illustrate this point. However, while statistics are staggering, numbers do not represent the heart of the Needed approach. The Needed approach emerges through the experiences of individuals. The women who represent the 1 in 6 struggling to conceive.⁶³⁶ The men and women who place heavy burdens on their financial futures in efforts to grow a family through fertility treatments. The women whose perinatal health and experience is diminished by complications during pregnancy and delivery. The women who struggle with PPD and must grieve the loss of motherhood expectations in tandem. The families who feel the immense weight of a neuropsychologist's diagnosis on paper stating their child has joined the 1 in 36 children with autism and the journey ahead.⁶³⁷ The women who were not empowered with the experience of optimized lifelong nutrition and thus a potent agent of control against such adverse events.

In the efforts to be a force of change for an idealized future for maternal and child health, the Needed approach aims far beyond the simplistic incorporation of nutritional supplementation in the perinatal period. The Needed approach supports comprehensive nutritional and health assessments on women of diverse backgrounds to better grasp the current state of perinatal nutrition status and identify critical areas for intervention. The Needed approach supports the ongoing research to recalibrate our understanding of women's nutritional needs from preconception and beyond lactation with distinct focus on both maternal and fetal health outcomes. The Needed approach supports the research which will grow our understanding of nutritional and health indicators with respect to establishing perinatal reference ranges. Such an approach must seek to incorporate bioindicators of nutrient status and genomics assessments which reflect holistic nutrient utilization and synergy among nutritionally essential pathways as well as key findings from robust health screens which lend to a comprehensive understanding of present status. The Needed approach maintains an understanding and appreciation for the complexity of factors which contribute to the widespread presence of inadequate perinatal nutrient status. Therefore, the Needed approach supports the intentional and careful provision of nutrients through supplementation for women preconceptionally and beyond lactation. However, this approach is food-first and is actualized through the inclusion of a nutritional professional to guide interpretations of assessments and provide holistic support

through interventions. Thus, the Needed approach exemplifies a commitment to place the control of a woman's lifelong health and intergenerational health outcomes back into the hands of women. This is a crucial move away from an emphasis on providing nutrients for deficiency prevention and towards harnessing nutrition for health optimization. The Needed approach represents a commitment to rigorously assessing the efficacy of our strategy in diverse populations and maintaining a flexibility in our approach as knowledge expands and shifts to optimally support maternal and offspring health.

Conclusion

Needed has done the research and is well positioned to challenge the status quo regarding the current perinatal dietary recommendations and nutrition standards. The comprehensive evidence which has powered the formulation of the Needed approach can bridge the gap between the complexities of present dietary inadequacies in the perinatal period and nutritional recommendations which are grossly lacking in population-specific evidence. Needed has elevated the standards for perinatal supplements through the eyes of the evidence with optimized formulations to enhance bioavailability across a spectrum of known conditions and environmental stressors. Needed is now on a path to radically shift the present and broken perinatal nutritional paradigm. The vision to ultimately revolutionize perinatal nutrition will be realized through the advancement of the Needed approach to engage both high-quality research through Needed Labs and to establish a nutritional care model within our framework, Needed Nutritional Care™. Needed Labs will gather foundational evidence to inform real-world decisions around nutritional optimization in pregnancy. But we are not just researching, we are implementing change. In partnership with GrowBaby Health, Needed Nutritional Care™ will serve as a crucial complement to perinatal care by empowering women with an understanding of their individual nutritional needs and how to implement dietary interventions to optimize their pregnancy and health of their future child(ren). The GrowBaby Health care model has demonstrated over a decade of positive outcomes for maternal and infant health, with measurable improvements in preterm birth, gestational diabetes and hypertension rates among pregnant women. These pillars of the Needed paradigm will generate crucial evidence and provide holistic support for women in a cyclical framework, such that we are consistently growing and progressing with the evidence and diverse needs of women in perpetuity. Needed is more than a brand name, it's a detailed and critical assessment of the current landscape for perinatal nutrition, and the intent to revolutionize this space to empower individuals for optimal perinatal health.

Abbreviations

DOHaD, Developmental Origins of Health and Disease; US, United States; NHANES, National Health and Nutrition Examination Survey; WHO, World Health Organization; MTHFR, methylenetetrahydrofolate reductase; NTD, neural tube defects; SNPs, single nucleotide polymorphisms; FDA, US Food & Drug Administration; EAR, estimated average requirement; AI, adequate intake; RDA, recommended dietary allowance; UL, tolerable upper intake level; IAAO, indicator amino acid oxidation; PUFAs, polyunsaturated fatty acids; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ALA, alpha-linolenic acid; ACOG, American College of Obstetricians and Gynecologists; PPD, postpartum depression; SCFAs, short-chain fatty acids; SGA, small for gestational age; GDM, gestational diabetes; THF, tetrahydrofolate; 5-methylTHF, 5-methyltetrahydrofolate; SAM, S-adenosylmethionine; RBC, red blood cell; USPSTF, US Preventive Services Task Force; EFSA, European Food Safety Authority; AdCbl, adenosylcobalamin; MeCbl, methylcobalamin; PLP, pyridoxal 5' phosphate; FMN, flavin mononucleotide; FAD, flavin adenine dinucleotide; PC, phosphatidylcholine; PEMT, phosphatidylethanolamine N-methyltransferase; 25[OH]D, 25-hydroxyvitamin D; MK-7, menaquinone-7; BMI, Body Mass Index; GLUT1, glucose transporter isoform 1; LDL, low-density lipoprotein cholesterol; GLP-1, glucagon-like peptide 1; ADA, American Diabetes Association; OGTT, oral glucose tolerance test; HoloTC, Holotranscobalamin; MMA, methylmalonic acid; 1,25(OH)2D, 1,25 dihydroxyvitamin D; CDC, MTF-1, metal-responsive transcription factor 1; Centers for Disease Control and Prevention; UIC, Urinary iodine concentration; SIC, serum iodine concentration; L, lutein; Z, zeaxanthin; AMD, age-related macular degeneration; AREDS2, Age-Related Eye Disease Study 2; L-ZIP, Lutein and Zeaxanthin in Pregnancy; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance

Note. Visuals were created using Biorender.com and Canva.

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