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Development of a Plant-Based Dietary Supplement to Address Life-Cycle Needs of the European Female Population

Sara D Garduno-Diaz*, Ramona Milcheva and Chanyu Xu

ONO Labs, Berlin, Germany

***Corresponding author:** Sara D Garduno-Diaz, ONO Labs, Berlin, Germany, **E-mail:** sara@onolabs.com

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Abstract

Peri-natal micronutrient supplementation is commonly recommended to optimize maternal-child health outcomes in Europe. While a healthy diet remains the path of choice for nutrient intake, supplementation is often necessary to ensure adequate micronutrient intake. With the growing preference for non-synthetic ingredients and the increased market for non-animal-based products, this work describes the process followed for the development of a plant-based multiple micronutrient supplements targeted at women at different stages of their life cycle. A list of key nutrients for inclusion was prioritized, based on the existing literature on nutrient needs for women, as well as on their most pressing wellbeing needs. This was followed by the identification and selection of qualified raw ingredient providers. The final line of products included three multiple-micronutrient supplements meeting the following criteria: vegan, gluten-free, lactose-free, and without artificial conservatives. Microbiological control was carried out three-fold, once by the raw material providers followed by double independent laboratory analysis of the end-product micronutrient supplement. This was then tested for human factor contamination, pesticides, total aerobic microbial count, total yeast count, and total mold count. Emphasis was placed on meeting product standards for the European Union, and specific requirements for the German market in food and pharma. Best practices were observed during the process to achieve multiple quality standard accreditations. In addition, organoleptic properties were adjusted in accordance to the female market demands. The results presented here reach the point of introduction of the newly developed product to the market, with acceptability and effectiveness results to be published at a later date.

Keywords: Women's health; Micronutrient supplement; Pregnancy; Lactation; Healthy eating

Introduction

Alteration in the nutrient status caused by insufficiencies of vitamins and minerals is also known as "hidden hunger" [1], since most people affected by it do not show the classic symptoms associated with hunger and malnutrition. While it can be generalized that in Europe there is no shortage of food supply [2], and poverty levels are relatively low in comparison to other regions of the World, less poverty does not always mean better-nourished people. While a healthy diet remains the path of choice for nutrient intake, supplementation is often necessary to ensure adequate micronutrient intake. Women of reproductive age, and especially pregnant women, are recognized to be at risk of multiple micronutrient deficiencies, such as iron, folic acid, iodine, zinc, Vitamins A and D, riboflavin, B6 and B12, with the likelihood of adverse effects on the mother and pregnancy outcomes [3]. It has been suggested that on a population level, nutritional requirements for folate, as with those for Vitamin D, cannot be completely covered by a "varied diet", as recommended by national health authorities [4]. As recommended by Bhutta ZA et al. [5], multiple micronutrient supplementations for pregnant women may be one of the essential nutrition-related actions to take on the road towards universal health improvement.

Peri-natal micronutrient supplementation is commonly recommended to optimize maternal-child health outcomes in Europe. Often, highest concern is for iron [6], folate [7], and essential fatty acids [8], due to their importance in the development of the fetus [9] from early in the pregnancy until well into the lactation stage. It has also been suggested that more attention needs to be paid to Vitamin B-12 status of women during pregnancy and lactation [10]. The cause of these low plasma Vitamin B-12 concentrations is most likely low dietary intake of the vitamin. While it is commonly believed that only strict vegetarians (vegans) are at substantial risk of developing Vitamin B-12 deficiency, several studies have revealed that even lacto-ovo vegetarians [11], or individuals who consume low amounts of meat [12], have lower plasma Vitamin B-12 and are at greater risk of Vitamin B-12 deficiency compared with omnivores. Vitamin D status of pregnant women should be of greater concern even in industrialized countries. In Germany, Vitamin D intake from both diet and supplements has been found to be below desired levels for both men and women [13]. Even moderately low plasma 25-hydroxyvitamin D concentrations observed in Parisian women at the end of winter were associated with poor fetal and infant skeletal growth and mineralization, and poor infant tooth mineralization. Although there is modest evidence to support a relationship between maternal 25(OH)-Vitamin D status and offspring birth weight, bone mass and serum calcium concentrations, these findings are limited

by their observational nature (birth weight, bone mass) [14]. The main benefits of regular supplementation during pregnancy include: the prevention of maternal complications and the reduction in other adverse pregnancy outcomes such as small-for-gestational age births, low birth weight, stillbirths, perinatal and neonatal mortality [15]. Nevertheless, due to the sensitive nature of these life stages, pregnant and lactating women must be hyperaware of the origin and quality of any substance consumed, including all dietary supplements.

With the growing preference for non-synthetic ingredients and the increased market for non-animal-based products, this work describes the process followed for the development of a plant-based, multiple micronutrient supplement targeted at women.

Methods

A list of key nutrients for inclusion was prioritized, based on the existing literature on nutrient needs for women, as well as on their most pressing wellbeing needs. Nutrients were grouped into vitamins, minerals, essential fatty acids and phytonutrients. The recommended dietary reference values corresponding to each nutrient was consulted and targeted using the guidelines set out by the European Food Safety Authority [16]. Specific recommendation levels for nutrient requirements during pregnancy and lactation when used when available; when not, adult intake levels were used in lieu.

The prioritization of nutrients was followed by the identification and selection of qualified raw ingredient providers. Mainly, this was controlled by requiring the potential raw ingredient providers to submit quality, origin and procedural certificates along with their tenders. Certificates included eco-quality, organic labels, fair-trade, vegetarian-approved, good-manufacturing practices certificates, soil association labels, and ISO 9001 certification when available. Six suppliers were included in the final list of raw ingredient providers from an initial identification of 230 potential providers. The full development process can be seen in figure 1.

Quality management was a multi-staged procedure as described in figure 2. Each raw ingredient was analysed independently, followed by an analysis of the full product. Microbiological control was carried out three-fold, once by the raw material providers followed by double independent laboratory analysis of the end-product micronutrient supplement. Each batch was tested separately immediately before product production, as opposed to relying in previously acquired laboratory results for the same ingredient or provider. The final products were then tested for human factor contamination, pesticides, total aerobic microbial count, total yeast count, and total mold count. Emphasis was placed on meeting product standards for the European Union, and specific requirements for the German market in food and pharma. Best practices were observed during the process to achieve multiple quality standard accreditations (under process as of the submission date of this publication). In addition, organoleptic properties were adjusted in accordance to the female market demands. This included the number and size of capsules to be used as the indicated daily portion for each product.

In addition to the micronutrients, each product contains a source of additional phytonutrients from three novel sources: maca (organic raw powder, root of *Lepidium peruvianum* Chacon), moringa (organic raw powder, leaf of *Moringa olifeira*), and chlorella (organic powder).

Results

The final line of products includes three multiple-micronutrient supplements meeting the following criteria: vegan, gluten-free, lactose-free, and without artificial conservatives. Each product contains specific nutrients targeting the various needs of women at three of their life stages: pre-pregnancy, pregnancy, and lactation. Each product contains 10 vitamins, 6 minerals, one essential fatty acid and a source of phytonutrients (maca, moringa, or chlorella) as listed on table 1.

Pre-pregnancy product

As characteristically required during this life stage, this product was designed to fully meet the daily requirements of vitamin D and folate among others. The role of these two micronutrients at the early stages of fetal development have been documented [17,18], and their increased intake may benefit women at an early stage of pregnancy, when other signs and symptoms may not be present yet [19].

Pregnancy product

In addition to the folate and Vitamin D which continue to be supplemented from the pre-pregnancy product, this second stage of supplementation is highlighted by the presence of vitamins from the B group. While most attention has been focused on a few micronutrients, for example iron and folate, multiple micronutrient deficiencies occur simultaneously when diets are poor. Some of these deserve more attention as possible contributors to poor pregnancy outcome, including B vitamin deficiencies [20]. Further, folate supplementation may be necessary during this life stage since natural food folates have a limited ability to enhance folate status as a result of their poor stability under typical cooking conditions.

Lactation product

In lactation, maternal status or intake of the B vitamins (except folate), Vitamin A, selenium and iodine strongly affect the amount of these nutrients secreted in breast milk. This can result in the infant consuming substantially less than the recommended amounts and further depleting stores that were low at birth [21]. For that reason, the product that was developed for the lactation stage covers not only the vitamins from the B group, but also approximately a quarter of the daily needs for non-organic micronutrients including iron, chromium, molybdenum, zinc, copper and manganese. In addition, soon-to-be mothers can benefit from the newly developed lactation product as it contains moringa. Moringa is one of the richest plant sources of Vitamins A, B, C, D, E and K. The vital minerals present in Moringa include Calcium, Copper, Iron, Potassium, Magnesium, Manganese and Zinc [22]. It has more than 40 natural anti-oxidants. Further, it has been shown to aid in the production of breast milk.

Essential fatty acids

During pregnancy, essential long-chain polyunsaturated fatty acids (LCPUFAs), including docosahexaenoic acid (DHA), play important roles as precursors of prostaglandins and as structural elements of cell membranes. Adequate consumption of omega fatty acids is vitally important during pregnancy as they are critical building blocks of fetal brain and retina. Throughout gestation, accretion of maternal, placental, and fetal tissue occurs and consequently the LCPUFA requirements of pregnant women and their developing fetuses are high [23] and may not be met by diet alone. For that reason, 20 mg of DHA have been included in each of the newly developed supplements as illustrated on table 1.

Phytonutrients

Dietary survey data has revealed that the mean vegetable intake (including pulses and nuts) in Europe is 220 g per day. Mean fruit intake

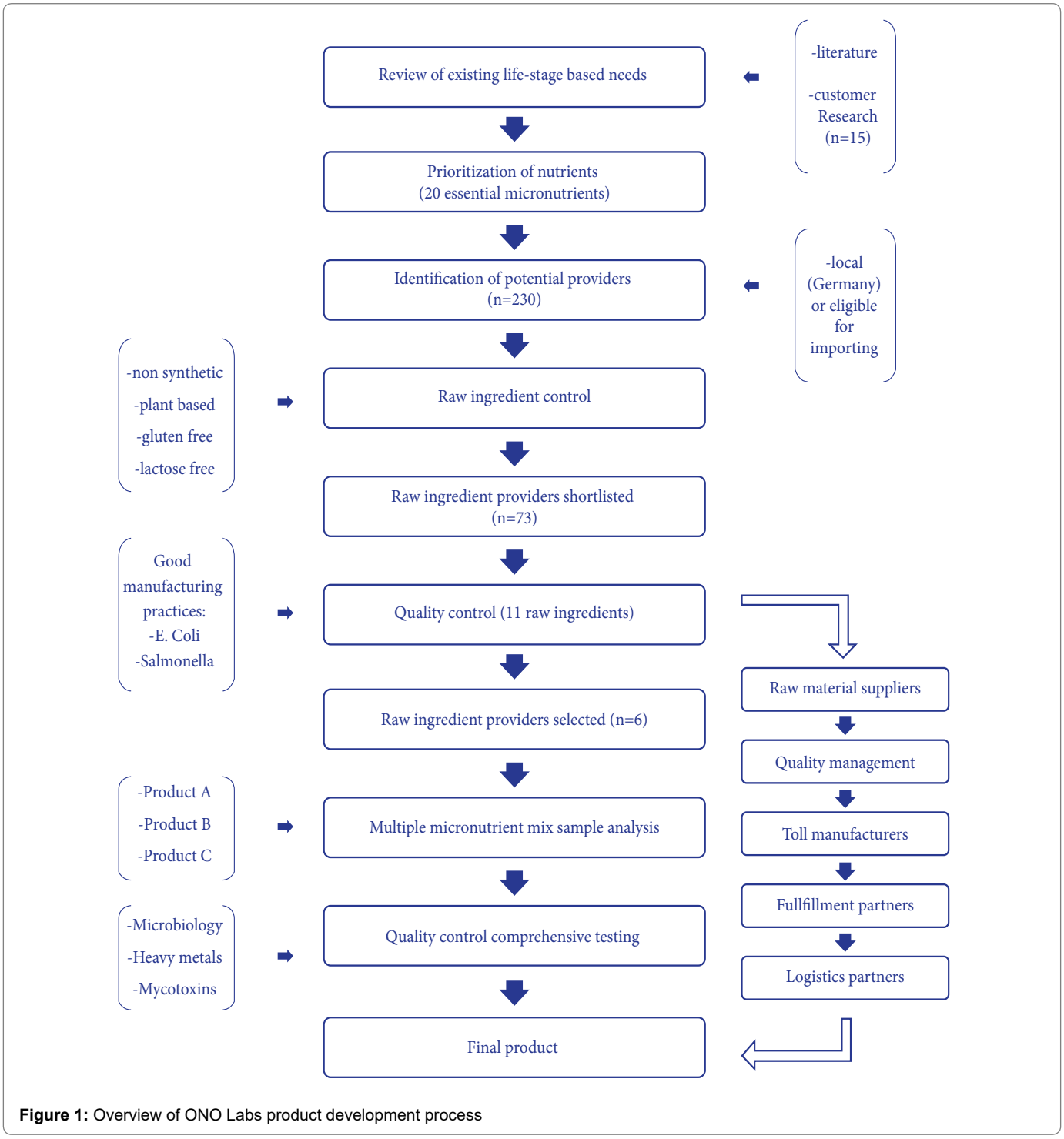

Figure 1: Overview of ONO Labs product development process

is 166 g per day, implying that the average consumption of fruit and vegetables is 386 g per day [24]. Fruits and vegetables provide vitamins, minerals and fiber, some energy (mainly in the form of sugar), as well as certain minor components-often referred to as phytochemicals or secondary plant products-which are potentially beneficial for health. The main sources of micronutrients found in the newly developed multiple-micronutrient supplements include maca, moringa, and chlorella. As part of the baby planning phase, maca can help a woman become pregnant faster by increasing fertility, overall vigor and energy levels [25]. The phytonutrients in macaare in the form of alkaloids, tannins and saponins, with the most likely to be responsible for its fertility-enhancing properties being p-methoxybenzyl isothiocyanate [25]. As a regulator of blood sugar levels, moringa can help a woman stay healthy and avoid pregnancy-related diabetes [26]. Phytochemical analyses have shown that its leaves are particularly rich in potassium, calcium, phosphorous, iron, vitamins A and D, essential amino acids, as well as such known antioxidants such as β-carotene, Vitamin C, and flavonoids [27,28]. In addition to meeting nutritional requirements, breast milk plays important roles in biodefense for nursing infants. Chlorella may help regulate the production of high-quality milk rich

Figure 2: Quality management controls at ONO Labs for ONO Natal line

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid. DHA, docosahexaenoic acid. Microbiology: Total number of colony-forming aerobic units, mesophilic sulfite-reducing clostridia, *Escherichia coli*, Biliary tolerant gram-negative bacteria, Salmonella, *Staphylococcus aureus*, fungi (yeasts and moulds), *Bacillus cereus*, Listeria monocytogenes. Heavy metals: mercury, arsenic, plumb, cadmium. Mycotoxins: aflatoxins B1, B2, G1, G2

Table 1: Percentage of daily nutrient intake covered by newly developed multiple micronutrient supplements

	Pre-pregnancy supplement	Pregnancy supplement	Lactation supplement
Vitamins			
B1	44%	36%	44%
B2	49%	41%	49%
B3	53%	44%	53%
B5	55%	46%	55%
B6	32%	27%	32%
B7	59%	50%	59%
B9	150%	276%	224%
B12	43%	36%	54%
D	100%	100%	100%
K	0.13%	0.13%	0.13%
Minerals			
Fe	16%	15%	21%
Cr	32%	30%	23%
Mo	32%	30%	23%
Zn	32%	30%	23%
Cu	32%	30%	23%
Mn	32%	30%	23%
Essential fatty acids*			
DHA	20 mg	20 mg	20 mg
Superfood source*			
Moringa	--	100 mg	--
Chlorella	--	--	200 mg
Maca	200 mg	--	--

Amounts shown as percentage of daily nutrient intake recommendations for the VO (EU) 1169/2011.
*no daily recommendation currently exists.
--not present in this supplement.
DHA: docosahexaenoic acid.

in immunoglobulins for lactation [29]. Chlorella is rich in amino acids, complex carbohydrates, vitamins, minerals, fatty acids, chlorophyll, carotenoid and pepsin [30].

Discussion

Maternal micronutrient status in the peri-natal period, and throughout pregnancy and lactation, should be viewed as a continuum; too often these 3 stages are treated and discussed separately from both a scientific and a public health perspective. Beginning prophylactic supplementation before pregnancy may help increase the likelihood of a positive childbirth experience. The most current evidence shows that giving multiple micronutrient supplements to pregnant women may reduce the risk of low birth weight and of small size for gestational age [31]. Deficiencies of micronutrients such as Vitamin A, iron, iodine and folate are particularly common among during pregnancy, due to increased nutrient requirements of the mother and developing fetus. These deficiencies can negatively impact the health of the mother, her pregnancy, as well as the health of the newborn baby. For vegan mothers to be the intake of Vitamin D and B12 are further areas on concern hence the most commonly available sources of these nutrients are animal-based. Further, Vitamin D is difficult to obtain from the diet, because it is not naturally present in many foods. Thus, people often rely on fortified foods and dietary supplements to meet their Vitamin D needs.

While multi-nutrient supplements are widely available in the market, the newly developed products presented here stand out for numerous reasons. One of the unique characteristics is the plant-based origin of all raw materials utilized in their composition. This makes all three products able to claim a natural origin, in addition to being free from synthetic preservatives, flavors and colors. Because these products are all plant-based the natural form of folate has been used, as opposed to folic acid, the more common synthetic form of the nutrient present in most available supplements. The products meet gluten and

lactose-free composition requirements, as well as being certified by the Made in Germany seal of quality.

A limitation of the present study is the unavailability of bioactivity studies. As the production remains at an initial stage these studies are expected to follow shortly.

Women's health

The continuum of a woman's life can be divided into several life stages with certain features characteristic of each stage, as depicted in figure 3. Biologically, the life stages of a typical woman are divided into infancy (before 12 years of age), puberty (adolescence, 12 years of age to late teens), sexual maturation (reproductive age, late teens to late 40s), climacteric period (late 40s to early 50s), and post-climacteric (elderly, 60+ years of age) years (Takeda, 2010). Some stages include fluctuations in the hormonal milieu as well as the life events specific to women, namely pregnancy. While strong attention is paid to the peri-natal stage in terms of nutrition, no practical recommendations to address their micronutrient needs are given in terms of quality, origin and composition of available supplements. Long-term studies in countries across the socioeconomic spectrum show that nutritional and psychosocial programs, implemented from pregnancy, have significant benefits for adult health and well-being, schooling and earnings, personal relationships and social life [32]. One mode of such nutritional programs is optimal nutrition. While the optimal mode of meeting recommended micronutrient intakes is an adequate diet and eating habits, in some situations supplementation is also important. The work presented here illustrates how supplements may be developed to tailor a woman's needs depending on her life stage. While for the time being the newly developed multiple micronutrient supplements are centered around the peri-natal stages of a woman's life, future products may target the main concerns of other life stages including securing nutrient stores before pregnancy and menopause, replacing nutrients lost through menstruation, and addressing age-related concerns such as reduced muscle mass and changes in skin elasticity. These various concerns, while significantly benefiting from an optimal diet, may require additional micro and macro nutrient supplementation.

Women as enablers for better nutrition

The World Health Organization's Every Woman Every Child initiative has highlighted the importance of women as enablers for better health at both a family and community level. Through their concept of Nurturing Care [33], women are able to make use of their skills as care givers in forms that until recently had been overlooked and underappreciated, as is the case with adequate nutrition from before birth. This critical developmental stage, with its life-long implications, may greatly benefit from advances in the food/nutrition/pharma fields.

Information is lacking on the optimal formulation of micronutrient supplements for pregnant women, and the need to continue these supplements during lactation is not recognized in many situations where maternal and infant health could benefit. For example, maternal intake of very-long-chain n-3 poly-unsaturated fatty acids during pregnancy and lactation may be favorable for the later mental development of children [8].

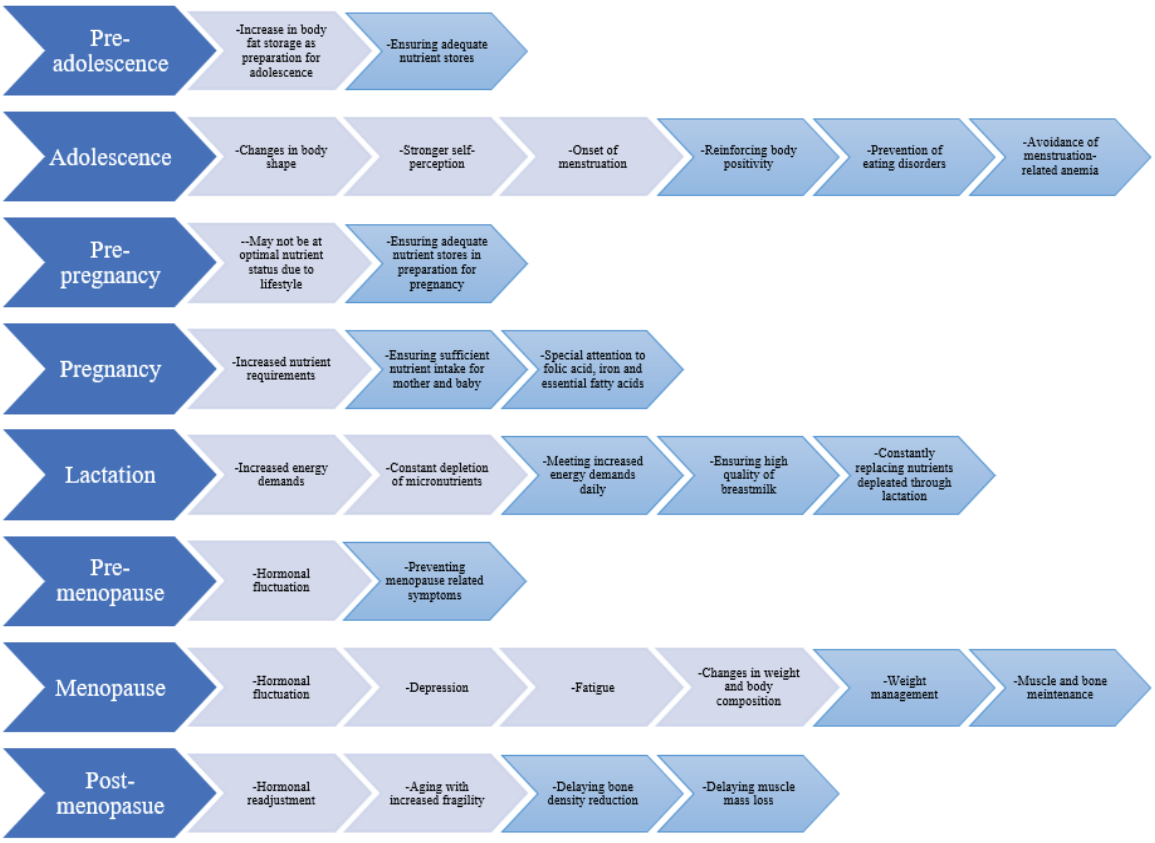

Figure 3: Women's life stages, characteristics and nutrient concerns

Similarly, once the lactation stage of a woman's life concludes, dietary supplementation tends to cease until otherwise requires, usually as a corrective measure post-menopause. Continuous supplementation as the aging process develops may be a sounder strategy from both an economic and health perspective when it comes to maintaining and improving women's health.

Various studies have found that by engaging women it is possible to engage whole communities [34]. That is, women become the entry way to healthier families, healthier communities, and healthier populations. In terms of nutrition supplementation, the practice may prove useful in two ways: first by creating awareness of the importance of nutrient coverage and the various stages of life, and second, by improving the health status of women, enabling them to better care for themselves, and other family and community members.

Author declaration

All authors participated in the study development.

Conflict of Interest

All authors are currently employed at ONO Labs.

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