Maternal serum docosahexaenoic acid (DHA) levels as a predictor of preeclampsia risk in urban and rural areas of developing country

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INTRODUCTION

Preeclampsia is one of the maternal health outcomes that can be influenced by nutritional status during pregnancy. Globally, preeclampsia affects 4.6% of all pregnancies and constitutes a significant contributor to maternal morbidity and mortality. Prior investigations have proposed that the administration of DHA supplements during pregnancy could offer a potential means to avert and manage specific pregnancy-related complications. Women living in urban and rural areas in developing countries, including Indonesia, may have poor food habits characterized by a low consumption of animal products. Pregnant women in urban areas were found to consume less meat, fish, and eggs. A lack of certain nutrients in the diet, such as docosahexaenoic acid (DHA), may also increase the risk of preeclampsia in pregnant women. This literature review aims to investigate maternal DHA levels as a predictor factor in preeclampsia risk in urban and rural areas of developing countries.

Well-recognized risk factors for preeclampsia either remain constant (e.g., age, parity, new paternity, extended birth intervals, a history of preeclampsia, and genetic factors) or are unalterable once a pregnancy has commenced (e.g., obesity, multiple gestation, and chronic hypertension). However, modifiable risk factors, such as dietary choices, might contribute to this condition’s development, offering a potential avenue for prevention.

An insufficient or excessive intake of specific nutrients in one’s diet, like docosahexaenoic acid (DHA), could elevate the risk of preeclampsia in expectant mothers. The body requires long-chain polyunsaturated fatty acids (LCPUFA) during pregnancy. It is advisable for pregnant women to incorporate a minimum of 200 mg of DHA into their daily diet, commencing no earlier than the 16th week of pregnancy. Sufficient LCPUFA consumption during the periconception and pregnancy periods is pivotal for fetal growth and development, with a particular emphasis on the development of the baby’s brain. LCPUFA also has a crucial role in maternal well-being since dietary omega-3 fatty acids have been associated with a reduced risk of adverse maternal outcomes linked to inflammation.

Additionally, examinations of the long-chain...
polyunsaturated fatty acid (LCPUFA) status during the first trimester of pregnancy have revealed that a significant proportion of pregnant women in Indonesia exhibit limited LCPUFA intake and blood concentrations. This includes eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and their precursor, alpha-linolenic acid (ALA). The study of the aetiology, prevention, and outcome of PE and other hypertensive disorders of pregnancy remains a healthcare research priority. Effective PE prevention would have significant health benefits and result in significant savings in health budgets. This literature review aims to examine the maternal levels of DHA as a possible risk factor for preeclampsia in both urban and rural areas of developing nations.

PREECLAMPSIA

Preeclampsia is a pregnancy-related condition marked by placental dysfunction and the maternal reaction to systemic inflammation, involving endothelial activation and coagulation. According to the definition provided by the American College of Obstetricians and Gynecologists, it is characterized by the presence of systolic blood pressure of 140 mm Hg or diastolic blood pressure of 90 mm Hg on at least two separate occasions, with an interval of at least 4 hours, along with the concurrent presence of proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral/visual symptoms occurring after the 20th week of gestation.

Preeclampsia has previously always been defined as hypertension and proteinuria that has just occurred when pregnant (new-onset hypertension with proteinuria). While these two criteria remain classic definitions of preeclampsia, it is worth noting that some women may experience hypertension in conjunction with other multisystem disorders, which signal the presence of severe preeclampsia even though the patient did not experience proteinuria. Meanwhile, edema was no longer used as diagnostic criteria because it is very often found in women with normal pregnancies.

EPIDEMIOLOGY AND RISK FACTORS OF PREECLAMPSIA

On a global scale, approximately 4.6% of pregnancies (with a 95% confidence interval ranging from 2.7% to 8.2%) are complicated by preeclampsia, which ranks among the top three causes of maternal morbidity and mortality worldwide. Over the years, numerous clinical and epidemiological studies have investigated the occurrence of preeclampsia in pregnant women across various countries and regions since 1967. A population-based study by Wang et al. from 1990 to 2019 (covering 204 countries and territories) revealed an increase in the incidence of high blood pressure during pregnancy, rising from 16.30 million to 18.08 million cases worldwide. This represented an overall increase of 10.92%. In 2019, the total number of deaths attributed to hypertensive disorders of pregnancy was approximately 27.83 thousand, reflecting a substantial decrease of 30.05% compared to the figures from 1990. Furthermore, the study unveiled a notable positive association between the incidence of preeclampsia and various sociodemographic factors as well as the Human Development Index (HDI) across all countries and regions in 2019.

Other meta-analysis studies have highlighted substantial variability in the incidence of preeclampsia. While preeclampsia is prevalent in both Eastern and Western developed countries, the highest incidence, coupled with the widest range of variability, is observed in developing nations. This considerable variability, often associated with sociodemographic factors evaluated through the Human Development Index, could contribute to the risk factors for preeclampsia. Zhang et al. elaborated on specific demographic, genetic, dietary, and environmental factors particularly pertinent in developing countries. These factors, including maternal age, educational level, dietary nutrient imbalances, and body mass index, have the potential to elevate the risk of preeclampsia during pregnancy.

ETIOLOGY, PATHOGENESIS, AND EARLY DETECTION RISK FACTOR OF PREECLAMPSIA

The current theory for the pathogenesis of preeclampsia is a two-stage model: impaired placental perfusion due to failure in placental vascular remodeling (Stage 1) leading to clinical manifestations of early onset of preeclampsia (Stage 2). Several factors can be involved in the failure of placental vascular remodeling, including abnormalities in trophoblast invasion, vascular endothelial damage, cardiovascular maladaptation, immunological phenomena, genetic predisposition, oxidative stress, environmental factors, genetics, and nutritional imbalances, whether in excess or deficiency.

Early detection of preeclampsia or preeclampsia screening aims to evaluate the presence of risk factors for preeclampsia and is carried out during antenatal examinations starting at 12 weeks of gestation. The latest paradigm was proposed by Poon et al., who described a two-stage strategy for identifying pregnancies at risk of preeclampsia. The initial stage involves evaluating the risk of early-onset preeclampsia (at 11-13 weeks of age), and the second stage is for the risk of late-onset preeclampsia (at 30-33 weeks).

A meta-analysis study states several risk factors for preeclampsia that can be assessed from early gestation (16 weeks), including multiple gestation, chronic hypertension, history of preeclampsia in previous pregnancies, diabetes mellitus, obesity, kidney disease and antiphospholipid syndrome. To promote a healthy pregnancy, expectant mothers should take proactive steps, such as maintaining their nutritional status, improving dietary habits by adhering to a recommended hospital diet, consuming nutritious foods, ensuring adequate rest, and engaging in appropriate physical activity. Moreover, it is worth noting that modifiable risk factors, particularly related to dietary choices, may contribute to the development of this condition and offer an avenue for prevention.
NUTRITIONAL FACTORS IN THE PATHOGENESIS OF PREECLAMPSIA

There has been a recent surge in interest in maternal nutrition’s role in the aetiology of PE. Based primarily on research conducted outside of pregnancy, it appears that specific nutrients may have a significant role in multiple critical stages in the current theories on the aetiology of PE. Numerous nutrients have significant roles in regulating endothelial function, especially folic acid, antioxidants, omega-3 (n-3) fatty acids, and L-arginine.

Docosahexaenoic acid (DHA) is classified as an essential fatty acid belonging to the omega-3 fatty acid family, specifically long-chain polyunsaturated fatty acids (LCPUFAs). These fatty acids are deemed essential because our bodies are incapable of producing them, necessitating their acquisition through dietary sources. LCPUFAs represent integral constituents of phospholipids present in all bodily tissues, and they actively participate in the functional regulation of cellular and subcellular membranes. This fatty acid (DHA) is composed of a 22-carbon acyl chain and is chemically denoted as all-cis-4,7,10,13,16,19-docosahexaenoic acid. Notably, DHA possesses an exceptionally low melting point, measured at -44 °C. It can be synthesized from the consumption of plant-based sources rich in alpha-linolenic acid (ALA) or directly obtained from foods containing DHA, such as fish, fish oil, eggs, crab, shrimp, and various meat products.

DHA SUPPLEMENTATION ROLE IN PREGNANCY

DHA supplementation is advised for pregnant women due to its neurological, visual, and cognitive benefits. Furthermore, the study suggests that supplementation can prevent and treat certain pregnancy complications. Long-chain omega-3 fatty acids (LCN-3), with a specific focus on DHA and its precursor, have been associated with a potential reduction in the risk of preeclampsia. According to existing information, testing for DHA levels could be conducted during either the first or second trimesters of pregnancy, affording adequate time to make adjustments to DHA intake as needed.

One study has demonstrated that DHA may have a role in reducing oxidative stress in conditions involving impaired placental development, which includes disorders like preeclampsia and preterm birth. Another study has revealed that DHA supplementation during pregnancy can notably decrease the risk of preeclampsia and severe preeclampsia. However, a systematic review and meta-analysis conducted by Bakouei et al. indicated that DHA supplementation during pregnancy does not significantly reduce the overall risk of preeclampsia. Nevertheless, this analysis suggests that DHA can be effective in preventing preeclampsia in pregnant women with low-risk factors.

Furthermore, this study’s results indicated that the optimal timing for DHA supplementation to prevent preeclampsia is during the first trimester of pregnancy. Providing DHA during the second trimester is considered late and appears to diminish the effectiveness of DHA in preeclampsia prevention. Some studies showed that DHA also has the ability to prevent apoptosis in the placenta, thereby reducing the risk of preeclampsia. DHA is considered to be more effective and powerful as an antioxidant and anti-inflammatory in preventing preeclampsia compared with the combination of DHA and EPA.

As a result, maintaining an appropriate fatty acid profile during both early and late pregnancy is of paramount importance for the well-being of both the mother and the child. DHA consumption was also different in rural and urban areas, women living in urban and rural areas in developing countries, including Indonesia, may have poor food patterns indicated by low consumption of animal products. Pregnant women in urban areas had low meat, fish, and egg intake. This food pattern may predispose pregnant women to the development of crucial nutrient deficiencies such as omega-3 fatty acids.

A recent review recommends a daily DHA intake of 200 mg during both pregnancy and lactation. It is essential to maintain a balance between DHA intake and arachidonic acid (AA) intake, as an excessive DHA intake may potentially increase the susceptibility to AA deficiency. Jakarta, being a multicultural city with a diverse range of educational and financial backgrounds, exhibits a variety of dietary fat sources. Over time, dietary preferences have shifted towards a “western diet,” characterized by a high content of omega-6 polyunsaturated fatty acids (PUFAs) but a low presence of omega-3 PUFAs. Consequently, this dietary shift has led to a substantial alteration in the ratio of these fatty acids, reaching a ratio of about 20:30:1.

DHA IN PREECLAMPSIA

DHA’s role, in particular, is vital for the development and functioning of nervous system cells in the developing fetus. Various factors influence the availability of DHA and EPA to fetal tissues, including dietary intake, endogenous synthesis from alpha-linolenic acid, transport within the bloodstream for delivery to placental tissues, placental tissue uptake, and transfer to cord blood. Multiple studies have indicated that levels of omega-3 fatty acids in the bloodstream are lower in mothers with preeclampsia during the third trimester or postpartum, in comparison to those with normal pregnancies.

Particularly docosahexaenoic fatty acid (DHA) in preeclampsia patients, there is a notable decrease in serum levels of vascular endothelial growth factor (VEGF), an angiogenic factor, as compared to pregnant women without preeclampsia. A deficiency in VEGF can cause endothelial dysfunction which will further interfere with the transfer DHA into cells. Preeclampsia patients usually have low DHA levels and show a deficiency of anti-inflammatory factors such as lipoxins and prostaglandins.

In individuals with preeclampsia (PE), significant alterations in maternal plasma DHA levels are observed. A study conducted by Dangat et al. involved the collection of peripheral blood samples from PE patients (n = 45) and normal pregnant women (n = 85) at the time of delivery. Their findings revealed a substantial reduction in maternal plasma DHA concentrations in PE patients. The decrease in DHA levels in cord blood could be attributed to one of three factors:
(1) PE patients might be exposed to an environment low in polyunsaturated fatty acids (PUFAs), resulting in a reduction in DHA content in maternal plasma and subsequently in cord blood; (2) Oxidative stress in placental tissues of PE patients may lead to the peroxidation of cord blood lipids. This oxidative stress can further cause dysregulation of angiogenic factors, resulting in an increase in soluble fms-like tyrosine kinase-1 (sFlt-1), which has been shown to induce oxidative stress and subsequently contribute to a decrease in DHA levels in cord blood; (3) Placental tissues from PE patients exhibit lower mRNA levels of delta-5 desaturase and fatty acid transport protein 1/4 (FATP1/4).19

Though the precise mechanism remains shrouded in uncertainty, the existence of misplaced fat within the placenta implies a potential entrapment of DHA, hindering its transfer to the fetus and ultimately resulting in reduced DHA levels in cord blood. Among the family of fatty acid transport proteins, encompassing fatty acid-binding proteins (FABPs) and fatty acid translocases (FAT/CD36), FABPs predominantly inhabit the maternal-facing placental membranes in human placental tissue, while FATPs and FAT span both maternal and fetal membranes. Nevertheless, during pregnancy, the supplementation of DHA appears to mitigate the decrease in cord blood DHA levels linked to these potential factors. Firstly, the introduction of exogenous DHA supplementation may bolster the diminished maternal plasma DHA levels in preeclampsia (PE) patients. Secondly, DHA might exhibit antioxidative characteristics by fostering mitochondrial function and biogenesis, potentially curbing oxidative stress in PE patients. Thirdly, the control of FATPs and FABPs is influenced by peroxisome proliferator-activated receptor (PPAR-), with the chief natural ligand for PPAR- primarily deriving from dietary n-3 polyunsaturated fatty acids (PUFAs), with DHA emerging as the most vital component in this context.19

In cases of preeclampsia, the expression of genes associated with placental lipid transport, such as FATP 1 and 4, and fatty acid elongation (fatty acid desaturase 1), is significantly reduced. However, this reduction does not extend to other genes like fatty acid desaturase 2 and FABP-3. This implies that during preeclampsia, there is a potential reduction in the placenta’s capacity to transport lipids as well as synthesize DHA from alpha-linolenic acid (ALA) in placental tissue. Furthermore, when compared to normotensive pregnancy, severe preeclampsia is associated with a decrease in placental mRNA expression of MFSD2A, a transporter for DHA in the brain. Nevertheless, the impact of this reduction on fetal development remains uncertain. These findings collectively suggest that the transport and metabolism of omega-3 fatty acids are disrupted during preeclampsia. The observed reduction in omega-3 fatty acids in placental tissue and cord blood from mothers with preeclampsia, as compared to those with normal pregnancies, supports these findings. It remains unknown whether DHA levels in cord blood respond to increased dietary intake during preeclampsia.8

This pathogenesis aligns with the findings of Kulkarni et al., who noted that at delivery, plasma DHA levels were lower in preeclamptic pregnancies compared to normotensive pregnancies, and this difference was similarly observed in samples of infant cord blood. Given the low levels of maternal blood omega-3 fatty acids in preeclampsia, a significant question arises regarding whether the placenta can compensate by increasing the trafficking, synthesis, and transfer of omega-3 fatty acids.20 A study conducted by Hariraj in India also reported that serum DHA levels in pregnant women at 32 to 36 weeks of gestational age were significantly lower in mothers with preeclampsia when compared to normal pregnant mothers.26

The fatty acid composition of the placenta in preeclamptic mothers differs from that of normal pregnancies. Specifically, in mothers with preeclampsia, there is a consistent reduction in the concentrations of DHA and total omega-3 fatty acids in both the central fetal and maternal regions of the placenta.825 However, meta-analyses failed to show a reduced risk of preeclampsia associated with higher LCPUFA intake.27

MATERNAL SERUM DHA LEVEL MEASUREMENT

For the effective connection of dietary n-3 (omega-3) long-chain polyunsaturated fatty acid (LCPUFA) status to clinical outcomes, reliable biomarkers are essential. However, the lack of studies investigating the blood concentration of LCPUFA in pregnant women in developing countries, particularly in Indonesia, can be attributed to the high cost of examination and procedures, as well as the absence of standardized approaches for fatty acid analyses that are commonly utilized.

The omega-3 index, which quantifies the percentage of EPA and DHA in erythrocytes through standardized analysis, serves as a common indicator for assessing an individual's EPA and DHA status. This index is measured in numerous laboratories worldwide and can be determined using a straightforward home blood test kit or more advanced gas-chromatography/mass spectrometry (GC-MS) for a comprehensive evaluation of all fatty acid components. However, even minor differences in analytical methods may lead to significant differences in results. No human subjects have an omega-3 index of less than 2%, indicating a critical minimum. Furthermore, clinical events correlate with levels rather than doses of EPA and DHA, and EPA and DHA bioavailability varies between individuals.28

Another method for measuring DHA is the ELISA method, which relies on a competitive inhibition enzyme immunoassay technique. In this assay, a microtiter plate is pre-coated with Docosahexaenoic Acid (DHA) protein. Subsequently, standards or samples are introduced into the corresponding wells of the microtiter plate, along with a biotin-conjugated antibody specific to Docosahexaenoic Acid (DHA). The concentration of Docosahexaenoic Acid (DHA) in the samples is determined by comparing their optical density (OD) to the standard curve.29

CONCLUSION

In conclusion, omega-3 long chain polyunsaturated fatty acids (LCPUFA), especially DHA, are believed to play a
crucial role in the processes of normal pregnancy implantation, placentation, and fetal development. They have also been associated with better maternal health outcomes, including a reduced risk of maternal complications related to inflammation, such as preeclampsia. Adequate intake of LCPUFAs during the peri-conception and pregnancy stages is vital to support proper fetal growth and development, particularly in terms of brain development. However, in the context of preeclampsia, the status of these fatty acids appears to be compromised, although direct causal links have yet to be established. During pregnancy, it is recommended that women consume at least 200 mg/day of DHA, with supplementation starting no later than 16 weeks into the pregnancy. Early detection of preeclampsia risk is also crucial. Numerous studies have demonstrated the high potential of docosahexaenoic acid (DHA) in effectively and safely reducing the risk of preeclampsia in pregnant women. Therefore, early assessment of an adequate fatty acid profile in both early and late pregnancy is of utmost importance for the well-being of both the mother and the child. This has been a challenging endeavor, particularly in developing countries, where variations in sociodemographic factors that influence dietary patterns can predispose pregnant women to critical nutrient deficiencies, ultimately increasing the risk of preeclampsia during pregnancy.

APPENDIX

The concepts of evidence-based practice are applied in the writing of this review in order to validate, justify, and/or improve clinical statements. The literature search was conducted using the keywords “DHA” and “preeclampsia” on clinical evidence search engines such as PubMed, ScienceDirect, Sci-hub, and Google Scholar. The author then sorts and screens the titles and abstracts before deciding to use literature as a reference source. The hierarchy of sources is determined by their level of evidence (I–VIII), where the primary source with the highest level of evidence is utilized.

CONFLICT INTEREST

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ETHICAL CLEARANCE

None.

REFERENCES


