



REVIEW

Periconceptional Mediterranean diet during pregnancy on children's health

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Keywords

Congenital defects • Mediterranean diet • Periconceptional period • Pregnancy

Summary

During pregnancy, rapid and subtle physiological changes are observed from conception to birth. Nutrition and other lifestyle factors before and during pregnancy have been shown in the literature to influence the health of both mother and child. A healthy and varied diet during pregnancy can provide adequate energy and nutrients for both the mother and the growing fetus. Current research focuses on the periconceptional phase, which includes the early processes of gametogenesis, embryogenesis and placentation. A variety of abnormalities and pregnancy-related problems occur during this period, including congenital defects, fetal loss, miscarriage and preterm birth. A varied and balanced diet during periconception is important to maintain

fetal development and growth. To date, numerous studies have been conducted to investigate the effects of consuming different nutrients, foods or food groups during pregnancy on the health of mother and child. For example, the Mediterranean diet is considered as a balanced, nutrient-rich diet due to the low consumption of meat products and fatty foods and the high consumption of vegetables, cheese, olive oil, fish, shellfish and little meat. While many studies have been conducted in the literature to investigate the effects of a Mediterranean diet during pregnancy on fetal health, the results have been inconclusive. The aim of this article is to review the current literature on the Mediterranean diet during pregnancy.

Introduction

Pregnancy has a complex nature involving growth, development and maturity processes. From fertilization to birth, a whole range of processes take place to prepare the fetus for life outside the womb [1]. Inherited diseases or chromosomal aberrations has been a central aspect of perinatal research and neonatal health. However, recent studies have been conducted to investigate the interaction between mother and fetus from different angles [2]. Pregnancy consists of two main periods including the embryonic period and the fetal period. The embryonic period lasts eight weeks, the foetal period lasts from the ninth week of pregnancy until birth [1, 3]. The first two weeks of the embryonic period are crucial because the embryo is extremely sensitive to an unfavourable environment (changed hormone concentrations, inadequate blood and nutrient supply), and in certain situations prenatal mortality may occur. From the second until the eighth week, the embryo is very sensitive to teratogenic drugs as embryonic development is initiated at this period. Finally, important physiological adaptations and less severe morphological changes occur during the fetal period. This period is critical due to changes that result in fetal programming that conditions the optimal or problematic organ systems affecting the whole organism [3, 4].

Some of the physiological changes that occur during pregnancy result in an increase in plasma volume and red blood cells, and a reduction in concentrations of nutrient-binding proteins and micronutrients that circulate in the body [5]. Dietary intake, limited exercise, smoking and alcohol use are critical to the health of women and their children during pregnancy and breastfeeding [6, 7]. Nutrition is considered one of the most critical environmental elements influencing embryo and foetal development and maternal health [8]. During pregnancy, the need for nutrients increases to support the growth and development of the fetus and to maintain maternal metabolism [9]. In recent years, several studies and comprehensive meta-analysis have shown that inadequate intake of important macronutrients and micronutrients can adversely affect pregnancy outcomes and neonatal health [9]. Deficiencies in micronutrients, in particular, have been linked to an increased risk of infertility, fetal structural abnormalities and long-term illnesses [8]. Since pregnancy is composed of different phases that continue, maternal nutrition and hormones have a significant influence on all phases of embryonic and foetal development, maternal nutrition and hormones have a significant impact on all stages of embryonic and fetal development [10]. Importantly, the periconceptional period is considered as a critical period for fetal development and health. During this period, a variety of

abnormalities and pregnancy-related problems occur, including congenital defects, fetal losses, miscarriages and preterm delivery [11]. According to the literature, periconceptional nutrition has an impact on fetal development and growth. It is important that the intake of certain nutrients during pregnancy, especially, the Mediterranean diet (MD) is considered a healthy and balanced diet. A number of studies have proven that it helps to prevent maternal and fetal diseases during pregnancy [11, 12].

Pregnancy and diet

NUTRITION DURING PREGNANCY

Pregnancy is a 40-week period of life with different nutritional requirements for mother and child, and it is an important period of life for both. Pregnancy involves rapid and subtle physiological changes from conception to birth [7]. Diet and other lifestyle factors such as smoking and alcohol consumption before and during pregnancy and lactation have been shown to affect child health [13]. In addition, an unbalanced diet during pregnancy has been associated with serious pregnancy complications [14]. Although the role of nutrition in pregnancy has been investigated in several studies, the results have been inconclusive [15].

A healthy and varied diet during pregnancy can provide adequate energy and nutrients for both the mother and the growing fetus [5]. Several studies that investigated the effect of diet on pregnancy outcome focused on only one or a few nutrients [16]. High consumption of saturated fats, low consumption of polyunsaturated fats, carbohydrates and soft drinks, for example, have been associated with gestational diabetes mellitus (GDM) and hypertension [16]. In addition, calcium intake has been associated with a lower risk of preeclampsia and fewer preterm births [17]. Deficiencies in micronutrients such as folic acid, iron, and zinc and vitamins are common in pregnant women [18]. Low Fe consumption, for example, has been associated with anaemia, while low folate intake has been associated with neural tube abnormalities or preterm birth [7, 9]. Since vitamins and some minerals are important components of the immune system, deficiencies in these micronutrients can lead to harmful infections [8]. It is believed that micronutrient supplementation may be beneficial in preventing adverse pregnancy outcomes [19].

Extensive research has been conducted over the past decade to determine the relationship between intrauterine fetal development, postnatal phenotype programming and the risk of developing noncommunicable diseases including cardiovascular disease and neoplastic disease [20, 21]. An unfavourable nutritional status during pregnancy, namely reduced iodine, folic acid and protein intake, has been associated with intrauterine cerebellar development, altered cerebellar methylation patterns and higher lipoperoxidation in the children [22, 23]. In addition, consumption of fish and polyunsaturated fatty acids improved embryo morphology following *in vitro*

fertilization (IVF) treatment [24]. Currently, research focuses on the periconceptional period which is 14 weeks before and up to 10 weeks after conception and includes the early processes of gametogenesis, embryogenesis, and placentation [25]. Researchers have reported that an unhealthy maternal lifestyle during periconception has negative effects on reproductive outcomes [7, 26]. Importantly, reproductive failures occur during the periconceptional period, i.e. implantation failure, early pregnancy loss, miscarriage, congenital malformations in newborns, and fetal growth failure [26]. Maternal periconceptional nutrition affects fetal programming, placental cognition and fetal and maternal competition for food [27]. In addition, diet can influence embryonic development through biochemical signals in the environment of uterus. It has been shown that optimal nutrition during periconception promotes fetal growth and development [15]. Studies in animals and humans have shown that epigenetic events expressed later in adulthood are related to early embryonic stages and the quality of maternal periconceptional nutrition [7].

Notably, maternal one-carbon (I-C) metabolism plays an important role in the DNA methylation patterns of the offspring that influence postnatal gene expression and disease progression [26]. One carbon metabolism is altered by environmental factors such as inadequate folate and folic acid intake, lifestyle and medication use as well as common polymorphisms such as the methylenetetrahydrofolate reductase (*MTHFR*) C677T polymorphism [26, 28]. Consequently, genetic and environmental variables influence I-C metabolism as well as intrauterine DNA methylation, gene expression and the transcriptome may explain the association between maternal environment and long-term outcomes [20, 26]. In summary, the health of every human being from conception to adulthood requires a varied and balanced diet. The developmental processes already take place during pregnancy and are influenced by the mother's diet. Therefore, nutrition should be planned in order to avoid unfavourable pregnancy consequences.

MEDITERRANEAN DIET IN GESTATION

Fetal development depends on maternal nutritional and metabolic conditions. The baby's physiology and metabolism can be permanently altered and shaped by the intrauterine environment [29]. Several studies have investigated the association between the intake of various nutrients, foods or food groups during pregnancy and maternal and fetal diseases [30]. The Mediterranean diet, with its low intake of meat products and high-fat foods, is a balanced, nutritious diet that is considered a standard for diet quality because of its components such as vegetables, cheese, olive oil, fish, shellfish and little meat [31]. The health effects of this diet were described as early as the 1950s. The American scientist Ancel Keys was the first to note the effects of diet and lifestyle on cardiovascular disease [32].

The Mediterranean diet appears to provide adequate caloric and nutrient intake in appropriate amounts and proportions. It is distinguished by its high methyl donor content

for one-carbon metabolism, which is engaged in growth and programming activities, notably during the periconceptional period [33]. Many studies have been undertaken to investigate the effect of Mediterranean diet on maternal health and offspring health. For instance, the Mediterranean diet is associated with a higher chance of clinical pregnancy and live birth after IVF, and a lower incidence of infertility [34, 35]. A significant study undertaken by Australian experts found that the Mediterranean diet protects against hypertensive problems during pregnancy (HDP) [36]. Similarly, other studies found that diets rich in vegetables and fruits were associated with pre-eclampsia and gestational hypertension [37, 38]. In contrast, a higher risk of preeclampsia was observed in women who adhered to a Western diet [38].

In another study, higher consumption of animal proteins before pregnancy was linked to an increased risk of gestational diabetes, whereas higher consumption of plant-based proteins was linked to a lower risk of metabolic disorders [39]. Furthermore, in a study carried out in Iran, where the consumption of fast food is very high, it was found that the consumption of chips in particular increased the risk of gestational diabetes [40]. Sibling studies have shown that those who were exposed to a diabetic environment in utero have a higher risk of developing diabetes, regardless of whether they have a genetic predisposition [41].

Moreover, other studies that have examined the effect of diet on neonatal and fetal development have shown that children of women who have a diet rich in vegetables and fruits have a lower risk of developing congenital limb defects [42]. Similarly, the risk of developing orofacial cleft is lower in offspring of women who have a periconceptional diet rich in fruits and vegetables [43]. In addition, a “one-carbon” diet high in fish and seafood has been associated with a lower incidence of congenital heart disease (CHD) and septal abnormalities [43, 44]. In a study, eating lean fish during periconceptional period has been associated with higher risk of low birth weight [45]. Finally, several studies have found that the Mediterranean diet reduces the risk of small gestational age (SGA) in newborns [46, 47].

Although the impact of the diet on the health of pregnant women and offspring have not been clearly established, the benefits of the Mediterranean diet for mothers, fetuses, and offspring are well documented. This diet should be promoted before, during, and after pregnancy.

Mediterranean-style diet and common health problems in pregnancy

MEDITERRANEAN DIET AND GESTATIONAL DIABETES AND GLUCOSE INTOLERANCE

Gestational diabetes mellitus (GDM) is a glucose intolerance that occurs during pregnancy [48]. Depending on the diagnostic threshold and the population studied, 1-28% of all pregnancies are affected [49, 50]. GDM is associated with poorer pregnancy outcomes and a higher risk of maternal and child morbidity in the long

term [51]. Age of the mother and a family history of type 2 diabetes and obesity are among the nonmodifiable risk factors associated with GDM [52]. GDM, in particular, type 2 diabetes (T2D) has a genetic component and aggregates in families. It has been demonstrated that women who have a diabetic sibling have an increased risk of developing GDM [53, 54]. Furthermore, identifying modifiable risk factors linked with GDM is critical for developing effective preventative approaches and avoiding negative health effects [55]. Several studies focused on dietary components during pregnancy as one of the modifiable factors contributing to GDM [56]. High sugar consumption, for example, is thought to contribute to an inflammatory process that may be associated with insulin resistance [57]. Although a number of studies have been undertaken to determine the link between dietary patterns and GDM, the results have been inconclusive [58, 59].

Two studies found that eating high amounts of dietary fibre has been linked to lower risk of GDM, but this finding is not confirmed by other studies [60]. The results of another study show that a high glycaemic load in the diet contributes to the development of GDM [61]. Interestingly, several studies have been conducted to investigate the effects of fat subtypes on GDM [48, 62]. It was found that saturated fats are significantly associated with the development of GDM, while polyunsaturated fats may be protective against GDM. On the other hand, information from observational studies suggests that a healthier diet, such as a Mediterranean diet, reduces the risk of GD [58, 63].

The MedDiet Project addresses the importance of the Mediterranean diet, highlights that eating fruits, vegetables and whole grains may have preventive effects on GDM. A meta-analysis documented an important correlation between the risk of developing GDM and vitamin D deficiency [64]. A case-control study composed of 299 pregnant women diagnosed with GDM showed that adherence to the Mediterranean diet before pregnancy was associated with a lower risk of GDM [65]. Another study of 1076 pregnant women who followed a Mediterranean diet found a lower incidence of GDM and improved glucose tolerance [66].

Maternal Mediterranean diet and fetal/neonatal insulin sensitivity

Insulin resistance impairs glucose metabolism, resulting in decreased glucose uptake in various tissues. It is well established that the intrauterine environment affects the growing offspring in a variety of metabolic ways, ranging from metabolic health to the development of metabolic diseases [67]. Intrauterine environment, glucose homeostasis and insulin homeostasis have been shown to be affected by maternal diet. Pregnancy independent of maternal diet is characterized by increased development of insulin resistance, which may contribute to the development of GDM and some complex diseases in offspring later in life [68].

Importantly, animal studies have demonstrated changes in placental lipid transfer as a function of uterine lipid concentration and uterine circulation [69]. An increase in saturated fat in the womb has been shown to decrease insulin sensitivity and increase the glucose/insulin ratio in the child, resulting in inefficient glucose excretion. Insulin sensitivity has been found to increase with higher levels of omega-3 fatty acids. In addition, increased level of perinatal omega-6 fatty acids have been associated with the incidence of obesity in rodents [70]. Because the Mediterranean diet is high in monounsaturated fatty acids (MUFA), it has been shown to reduce the risk of cardiovascular disease by improving insulin sensitivity and blood lipids [71]. Another study highlights the importance of dietary habits in early pregnancy. Inadequate nutrition has a major impact on metabolic changes that cause prediabetic features at birth [72].

Maternal Mediterranean diet and neonatal lipoprotein profile and homocysteine

The studies mainly present findings on lipids and lipoproteins from infancy through adolescence and maturity. The presence of a proatherogenic environment, such as hypercholesterolemia during pregnancy, has previously been shown to increase oxidized lipids in the fetus and at birth. According to one study, lipid streaks grew relatively minimally during pregnancy, but their extent increased rapidly in later life compared to fetal development [73, 74].

Hyperhomocysteinemia is associated with the development of degenerative diseases such as kidney disease and neurological disorders. Therefore, in recent years, researchers have paid more attention to total homocysteine in serum [75]. For example, atherosclerosis is still a major cause of morbidity and mortality around the world [73]. There is evidence that the atherogenic process begins and is accelerated when levels of oxidised low-density lipoprotein (oxLDL) are elevated during pregnancy [2].

To date, the relationship between Mediterranean diet and many diseases has been studied. It has been suggested that inadequate consumption of Mediterranean diet is associated with lower risk of developing degenerative diseases. However, the effects of the Mediterranean diet on coronary heart disease during pregnancy have not been adequately studied [73]. Mothers who follow a Mediterranean diet during pregnancy have been found to give birth to infants with low levels of insulinemia and insulin resistance [76]. Moreover, in recent years, research has focused on paraoxonase (PON-1) enzyme since it has antioxidant features and prevents low-density lipoproteins (LDL) from oxidation. Also, it has been suggested that this enzyme has pleiotropic antioxidant effects [77]. Furthermore, it has been observed that semisynthetic diets may contain compounds such as proteins, fiber, minerals, and vitamins that may affect lipids and lipoproteins. In one study, adherence to a Mediterranean diet during pregnancy was associated with lower homocysteine levels in

Brazilian newborns [78]. In another study, following the Mediterranean diet was found to affect lipoprotein levels. A decrease in homocysteine levels was also observed, which was associated with improved glucose metabolism and higher maternal body weight [73].

Pregnancy and lipoprotein-associated coronary heart diseases

Undernutrition of fetuses in middle to late gestation results in inappropriate fetal growth, and leads to coronary heart disease [79, 80]. In particular, total fatty acids in plasma are significantly related to lipoprotein metabolism. In addition, several lipoprotein components such as cholesterol and saturated fat have been shown to be associated with cardiovascular health [81, 82].

Maternal hyperinsulinemia and increased tissue insulin sensitivity are some of the mechanisms leading to maternal fat deposition in the early stages of pregnancy [70, 73]. In later stages of pregnancy, low levels of lipoprotein lipase (LPL) and postheparin LPL activities are observed [70]. Changes in these metabolic processes reduce fat accumulation in maternal adipose tissue. Thus, increased lipolytic activity of adipose tissue leads to increased breakdown of fat deposits developed during the first trimester of pregnancy. In the liver, free fatty acids and glycerol are converted to acyl-CoA that leads to formation of glycerol-3-phosphate and triglycerides (TG), and packaged into very-low-density lipoprotein (VLDL). In addition, lipolysis increases and VLDL is produced and excreted in large amounts in later stages of pregnancy due to insulin resistance [70].

These metabolic processes in late pregnancy lead to an increase in VLDL levels and consequently, VLDL-TG and TG levels. In some pregnant women, transport of VLDL by cholesterol leads to an increase in total plasma cholesterol at the end of pregnancy. The increased level of VLDL in the late stages of pregnancy could therefore explain the increase in total cholesterol (TC) [70]. It is also suggested that the dietary mechanisms controlling low-density lipoproteins are less significant during pregnancy than in the pre-pregnancy period. Since TC seems to be the result of the temporary metabolic situation during pregnancy, TC should have a modest value in the diagnosis in pregnancy [73]. Detection of high levels of TC, could be used to determine neonatal risk for developing cardiovascular disease (CVD) [83]. In another study, CVD risk markers such as TC were shown to be detectable at 4 years of age at birth and in the respective parents [84].

The association between diet and lipoproteins in the fetus and at birth have not been extensively studied for several reasons. One of the possible reason was that the average levels of TC are similar in different populations of newborns [73]. According to the results of a study, Mediterranean diet during pregnancy may have an effect on systolic and diastolic blood pressure in children. In addition, the Mediterranean diet during pregnancy correlated with lower leptin levels, which may predict lower fat mass and TG in children [85].

Mediterranean diet and fertility

The influence of lifestyle factors on reproductive success has been extensively documented. To date, the influence of diet on fertility has been studied, focusing on individual foods and food categories [86]. In several studies, specific diet types and food groups have been widely studied, but the results have been inconclusive. According to some researchers, pregnancy rates after IVF have been increased by following a healthy diet [87]. Specifically, women who strictly adhered to the Mediterranean diet were found to have a lower risk of not becoming pregnant. According to the literature, male diet can have an impact on fertilization. Importantly, consumption of whole grains, cereals, vegetables, and fruits in large quantities is significantly associated with fertility and treatment outcomes [88]. According to some researchers, the high content of vitamin B6, folic acid and vegetable oils in the Mediterranean diet is one of the factors that can explain the positive effect of the Mediterranean diet on fertility [34]. Although the results of several studies are conclusive, further studies are needed to investigate the effects of the Mediterranean diet on IVF success rate [89].

Folate mechanism and congenital structural anomalies and fetal demise

The importance of the intrauterine environment for early embryonic development has been emphasized in recent years. In particular, folic acid has attracted the interest of researchers due to its importance in a number of clinical conditions [90]. Folate is necessary for cellular processes such as nucleotide synthesis and DNA repair. Furthermore, it acts as a cofactor for enzymes involved in one-carbon metabolism. Folate plays a central role in cell division and it is required during pregnancy and infancy. Folate plays a central role in cell division and is needed during pregnancy and infancy. During pregnancy, fetal, placental and maternal tissues need more folic acid [91, 92]. Folic acid deficiency, on the other hand, is associated with a number of diseases comprising birth defects and neural tube defects [93,94]. With an incidence of 0.2-10 per 1000 live births, neural tube defects (NTDs) are among the most common congenital anomalies of the central nervous system [95]. NTDs are serious birth defects caused by the failure of closure of the neural tube around 28th day after conception [96]. Genetic and environmental factors are involved in the pathogenesis of NTDs. Although the pathogenesis of NTDs is not yet clear, deficiencies in one-carbon metabolism are thought to be one of the causes the formation of NTDs [97].

Infants with anencephaly and spina bifida show several complications during their lifetime [98]. Randomized clinical trials have shown that folic acid consumption by mother during periconception is significantly associated with a reduced risk of developing NTDs [99, 100]. In addition, folic acid may also protect against other congenital abnormalities such as preeclampsia [101]. Folic acid intake and a folic acid-enriched diet are recommended

by World Health Organization (WHO) and other government organizations in numerous countries for women of childbearing age. The incidence of NTDs was reduced by 50-75% with folic acid supplementation in the periconceptional period [102].

The synthetic version of the naturally occurring folates is folic acid (pteroylmonoglutamic acid) (pteroyl-L-poliglutamic acid). The basic difference between folic acid and folate is that the B9 vitamins differ in the amount of glutamate molecules they contain. Folates are found in many foods, primarily in green vegetables [103]. It has been shown that a maternal Mediterranean diet enriched with vitamin B12, niacin, iron and magnesium was significantly associated with spina bifida in the offspring [102]. In a study, western and prudent diets were compared. As a result, it has been shown that the children of women who followed the former dietary pattern were at higher risk for having cleft lip despite folic acid supplementation [102, 103]. Finally, a significant association was found between the risk of spina bifida (SB) and inadequate maternal consumption of a Mediterranean diet, possibly related to increased oxidative stress due to deficiencies of vitamins B6, B12, and folates [103].

Conclusion

In conclusion, pregnancy is a complicated process involving growth, development and maturation. Maternal nutrition's importance has undoubtedly been the subject of several studies, as it affects growth, maturation and fetal development. It has been shown that inadequate intake of essential macronutrients and micronutrients can negatively affect the outcome of pregnancy and neonatal health. Particularly, the periconceptional period is considered as a critical period for fetal development and health, as various malformations and pregnancy-related disorders occur during this time, including congenital anomalies, fetal losses, miscarriages, and preterm births. Importantly, a Mediterranean diet throughout pregnancy, especially in periconception, contributes to more appropriate growth from the first stage of pregnancy.

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Conflict of Interest

The authors have no conflict of interest to declare.

Author's Contributions

PT,HC conceptualized the content, and wrote the manuscript; MCE assisted with the revision of manuscript; PT

conceptualized the content and critically revised the manuscript. All authors read and approved the final manuscript.

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