

Mediterranean Diet during Pregnancy

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Contributor: Marcello Lanari, Carlotta Biagi

The traditional Mediterranean diet has been shown to be a healthy eating pattern that protects against the development of many diseases in adults and children. Pregnancy is a critical period of plasticity during which foetal development may be significantly influenced by maternal nutrition. In this review, we systematically summarized and discussed results of studies investigating the protective role of Mediterranean diet against foetal growth, prematurity, congenital pathologies, asthma and allergy. Although current data are insufficient and randomized control trials are needed, growing evidence suggests the beneficial effect of the Mediterranean diet during pregnancy on children's health. In this sense, strategies aiming to promote adherence to this dietary pattern might be of considerable importance to public health.

Keywords: Mediterranean diet ; pregnancy ; offspring ; child health

1. Introduction

The Developmental Origins of Health and Disease (DOHaD) hypothesis posits that in utero exposure plays a critical role in the risk of disease in adulthood. Maternal diet during pregnancy contributes to the in-utero environment ^[1]; nutritional stress/stimulus applied during critical periods of early development permanently influences organism's physiology and metabolism, with the consequences of this metabolic programming often being observed much later in life ^{[2][3]}. Although the DOHaD hypothesis is well documented in animals ^[4], evidence connecting maternal diet quality during pregnancy and offspring risk factors is scarce and inconsistent in humans. Most studies have investigated the associations of specific nutrients, foods, or food groups intake during pregnancy with offspring health without considering the overall diet ^{[5][6]}.

Foetal growth restriction (FGR) and risk of new-borns small for gestational age (SGA), prematurity, neural tube defects (NTDs), congenital heart defects (CHDs), gastroschisis, asthma and allergy, overweight and metabolic disorders represent leading causes of childhood diseases that are supposed to be connected to maternal nutrition.

FGR is defined as an estimated foetal weight or abdominal circumference below the 5th or the 10th centile according to gestational age (GA) and sex, and it affects about 5–10% of all pregnancies ^[7]. FGR is associated with an increased risk for childhood morbidity (mainly hypoglycaemia, developmental delay and infectious diseases) and with about half of all foetal deaths ^{[8][9]}. It is also associated with chronic diseases in adult life including coronary heart disease, stroke, type-2 diabetes mellitus, adiposity, metabolic syndrome and osteoporosis ^{[10][11]}. New-borns are considered SGA when their body weight is lower than the 10th centile according to neonatal growth curves adjusted for gestational age at delivery and sex ^[12]. Not all SGA new-borns are pathologically growth restricted, as a proportion of babies (18–22%) are constitutionally small but healthy ^[12]. However, FGR significantly overlaps SGA, and they are often considered as a single entity. FGR and SGA can arise from several maternal, foetal and placental problems ^[13]; however, maternal nutrition has been recognized as one of the most important environmental factors influencing foetal growth and development ^{[14][15][16][17]}.

Preterm birth is defined as any birth before 37 weeks of GA ^[18]. Preterm birth, especially before 34 weeks of GA, is the leading cause of perinatal morbidity and mortality in developed country ^[19]. There are multiple risk factors for premature birth including having a previous premature birth, pregnancy with multiple babies, infection, drug or alcohol use, and age. A well-balanced diet during pregnancy has been reported to reduce the odds of a premature birth ^[20].

NTDs are a major health burden that affect 0.5–2/1000 pregnancies worldwide and represent a preventable cause of stillbirth, infant death and significant lifelong morbidity ^[21]. CHDs and gastroschisis are other common malformations representing major causes of mortality, morbidity and disability of perinatal origin ^{[22][23]}. The aetiology of these congenital malformations is multifactorial and both genetic predisposition and environmental influences contribute to them, with nutritional deficits serving as potential contributing factors ^{[24][25]}.

The prevalence of asthma and allergic diseases (atopic dermatitis/eczema, allergic rhino-conjunctivitis) has increased worldwide over the past few decades with the highest incidence occurring in children [26]. Globalization and consequent deviation from traditional to Western diet might be one of the environmental changes involved in the recent increased of the atopic diseases. In fact, decreased antioxidant (fruit and vegetables), increased n-6 polyunsaturated fatty acids (PUFA) (margarine, vegetable oil), and decreased n-3 PUFA (fish oil) intakes might lead to oxidative stress and inflammation and might contribute to the higher incidence of asthma and allergies [27][28].

Due to the importance of maternal diet during pregnancy as influencer of child health, actions to improve its quality are urgently needed. In this light, a good adherence to the Mediterranean diet (MD) could represent a good strategy. MD is characterized by increased consumption of unprocessed and plant foods, olive oil, and fish, whereas consumption of red meat, animal fats, sugars and salt are minimal. The MD is rich in mono-unsaturated fatty acids (MUFA), omega-3 PUFA and antioxidant polyphenols, and it is been recommended for its overall health benefits and potential for disease prevention [29]. Several observational and intervention studies support the role of the MD in preventing obesity, type 2 diabetes mellitus and metabolic syndrome in adults [30][31], while some recent studies suggest a protective role against obesity development in children [32][33][34]. In pregnancy, a higher adherence to the MD has been associated with lower risk of preterm birth, and higher birth weight [20].

2. Current Insights on Mediterranean Diet during Pregnancy

In the present review, we systematically summarized studies carried out to verify the protective effect on the offspring of maternal adherence to the MD during pregnancy. The initial search identified 602 studies, with 522 records excluded following abstract review. Of the 80 articles retrieved, 51 were excluded because of duplicates, reviews, letters, abstracts and articles without full-text in English language. In the end, 29 studies were included in the analysis. Included studies were published between 2008 and 2018. All but one of the 29 studies included in the review were observational (cross-sectional, cohort, and case-control) studies.

Although maternal nutrition has been recognized as one of the most important environmental factors influencing foetal growth and development [14][15][16][17], we found intermediate evidence linking maternal adherence to the MD pattern to FGR and risk of SGA new-borns, with cohort studies that reached the best scores for quality. A confirmation that adherence to the MD during pregnancy could represent a strategy for reducing the incidence of FGR and SGA new-borns could come from a randomized controlled trial that is recruiting patients in Spain [35]. This study is randomizing women at high risk for growth restricted foetuses into two different behavioural strategies program: a stress reduction program based on mindfulness techniques or a nutrition interventional program based on MD. The trial will last till February 2021.

We founded intermediate evidence supporting a protective effect of MD on preterm delivery, with cohort studies reaching the best scores for quality. The MD pattern, including low amount of sugars, could result in better blood glucose regulation during pregnancy. Although glucose intolerance is associated with a shorter duration of gestation independently of other known risk factors for prematurity [36], not all studies investigating the effect of MDA during pregnancy on preterm delivery found no significant correlation. The heterogeneity of results could be in part explained by differences in the definition of preterm delivery (<37 weeks versus earlier periods). Of note, the only randomized controlled trial found in the literature [37] showed that an early nutritional intervention with MD supplemented with extra virgin olive oil and pistachios significantly reduces the rate of preterm delivery.

Since long ago, many studies demonstrated that appropriate intake of folate during pregnancy can prevent the recurrence of NTDs [38]. Although it is known that the MD provides appropriate amount of folate, to date only two cross sectional studies [39][40] have investigated the effects of maternal adherence to the MD on NTDs incidence in offspring. Maternal MD adherence and risk of NTDs appeared significantly related, but the low number of studies reduces the level of evidence. In addition, it is not clear whether the MD protective effect is simply due to the correct folic acid intake or other MD components contribute as well. Anyway, to improve adherence to the MD in the periconception period could be considered a good strategy to reduce the incidence of NTDs. Regarding CHDs and gastroschisis, the number of studies is too low to draw any conclusion.

At present, there is low evidence of a link between maternal adherence to the MD and incidence of asthma and/or allergic diseases in the offspring. This is also due to quality coming from these studies was much more mixed, particularly for cohort studies. Additional studies are needed to better clarify the role of maternal adherence to the MD on this outcome.

Obesity and metabolic syndrome (MetS) are two of the most common chronic diseases among children. Recent evidence suggests these conditions have their roots in utero as maternal obesity, dyslipidaemia, and hyperglycaemia are

associated with child cardiometabolic health and developing insulin resistance and obesity later in life ^{[41][42]}. Although studies considered in this review indicate that higher adherence to the MD during pregnancy is a potential protective factor against abdominal obesity ^{[43][44]} and positively influences lipoprotein and homocysteine concentration ^[45], and insulin resistance in new-borns ^[46], the use of different endpoints to evaluate outcomes reduces the level of evidence.

Overall, most of the studies included in this review showed beneficial association between MD adherence during pregnancy and children's health. The strength of the association varied in the different health outcomes, and the level of evidence was affected by the high heterogeneity among the study design. Heterogeneity was mainly related to the methodology used for assessment of MD adherence. Epidemiological studies commonly use the FFQ to assess usual food consumption. Although an FFQ does not have the same accuracy as a dietary record or a 24 h dietary recall, it can reasonably report intake over a large period ^[47]. There are many kinds of FFQ, and not all have been validated. Anyway, they differ for the number of food items, the way of administration (self-administration or interviewer-administration), the quantification of consumed foods, etc. Furthermore, there are many ways to analyse results from FFQ, which are often used to extrapolate an index of overall diet quality based on an a priori scoring system ^[48]. The use of different scores for the assessment of adherence to the MD represents a possible confounding factor while comparing different studies.

In addition, the consumption rate of specific food groups was seldom considered. The so-called MD was inspired by the eating habits of people in the Mediterranean area (mainly Greece, Southern Italy and Spain). MD provides an optimal intake of "positive" nutrients (polyunsaturated fats, fibres, vitamins etc.) and a low intake of "negative" nutrients (e.g., saturated fats, sugars, sodium) through the proportionally high consumption of olive oil, legumes, unrefined cereals, fruits, and vegetables, moderate to high consumption of fish, moderate consumption of dairy products (mostly as cheese and yogurt), moderate wine consumption, and low consumption of non-fish meat products. The proportion of Mediterranean foods in the diet is different in different Mediterranean countries, even in people having the same level of adherence, and it largely depends on the characteristics of the study sample, i.e., ethnic origin of the enrolled population. Culture-driven dietary preferences vary among population and influence the intake of specific food subgroups. These differences are likely incompletely captured in the semiquantitative FFQ, particularly in their shorter version, because of the limited number of food items that are evaluated. Therefore, the sensitivity of MD adherence as predictor of children outcomes could be affected by regional variations of MD.

Another confounding factor is the stage of pregnancy considered for evaluation of adherence to the MD, as well as the time elapsed between the considered period and the administration of the FFQ. Not explored social and environmental factors could have a role.

How a good adherence to the MD during pregnancy could have positive effect in offspring not only during foetal life but also in later life is still unclear. The induction of epigenetics modification represents a possible explanation ^[49], but further studies are needed to confirm it. In addition to the epigenetics hypothesis, it is known that various nutrients may influence pregnancy outcomes by altering both maternal and foetal metabolism due to their roles in modulating oxidative stress, enzyme function, signal transduction and transcription pathways that occur early in pregnancy.

3. Conclusion

A good maternal diet quality in general, and the adherence to the MD in particular, are associated with a reduced occurrence of some negative outcomes in babies. Although it is still unclear whether an intervention to promote the MD could effectively reduce the prevalence of some childhood diseases, and randomized control trials are needed to better clarify it, current preconception care recommendations should carefully consider the benefit of MD, reinforcing advice on correct dietary habits. Strategies aiming to promote adherence to MD dietary pattern may be of considerable importance to public health. In addition, they have low cost and no side effects.

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