Review

Pregnancy eating habits and risk of tumor appearance in descendants in children and adolescents

Danai Theofilopoulou, Maria Tsouka, Eleni Panagouli, Theodoros N. Sergentanis, Artemis Tsitsika

MSc Program "Strategies of Developmental and Adolescent Health", 2nd Department of Pediatrics, "P. & A. Kyriakou" Children's Hospital, School of Medicine, National and Kapodistrian University of Athens, 115 27 Athens, Greece

ABSTRACT

Proper nutrition is generally defined as a diet that includes all food groups in balanced amounts. The Mediterranean diet is considered to be the standard diet, which seems to equip the human body with the necessary elements to prevent diseases. The present review included 46 surveys conducted during the period from 1995-2005. Research shows that nutrition plays an important role in pregnancy, as inadequate or excessive food intake has been associated with long-term and non-communicable diseases in the offspring. This literature review focuses on the role the diet followed by women during pregnancy plays and especially on the data related to its association with the occurrence of cancer in the offspring. The data highlight the diet of pregnant women as a potential factor in the occurrence of various types of infant or childhood cancer. In particular, micro and macro elements, such as carotenoids, caffeine, folic acid, vitamin C seem to have effects on the fetus when consumed by pregnant women and are involved in epigenetic processes. In conclusion, the advantages and limitations of the various studies were identified, as well as points that need further research.

Key Words: *cancer, leukemia, pregnant, infant, nutrition*

Corresponding Author: Maria Tsouka email: **mariatsouka596@gmail.com**

INTRODUCTION

A regular diet must include all food groups in balanced amounts, to be considered generally appropriate. Based on these data, the Mediterranean diet is considered as a balanced diet. According to its guidelines, the Mediterranean diet is characterized by a high intake of legumes, cereals, vegetables and fruits, high intake/ consumption of olive oil, low intake of saturated lipids, moderate intake of fish, low to moderate intake of dairy products (mainly in the form of dairy products) and low intake of meat and meat products. Therefore, the Mediterranean diet seems to meet all the criteria to be considered as a regular diet, both in terms of quantity and quality. The most important benefit of this diet is that it provides the necessary nourishing substances to pregnant women in order for the child has a reduced risk of developing diseases such as ALL (1).

From time to time, researchers have highlighted the correlation of the quantity of the pregnant woman's nutritional intake (insufficient/excessive nutrition) with long-term effects and occurrence of non-communicable diseases in children. Characteristically, a research conducted in 2017 by Luyckx et al. demonstrated that the development of a fetus in an obese intrauterine environment can permanently modify individual biological and metabolic pathways, resulting in adaptive pathophysiological alterations in the offspring and increased risks of non-communicable diseases in adulthood (2). The effect of the amount of nutritional intake of pregnant women was strengthened by other research data. The insufficient coverage of daily needs in vitamin C during pregnancy and the reduced ascorbic acid in the serum, appear to be associated with the risk of premature rupture of fetal membranes and premature birth (<37th week of gestation). In addition, the carbon metabolism cycle appears to be critical for the synthesis of DNA and RNA and the transfer of homocysteine to methionine and the formation of adenosylmethionine (SAM), which is the major methyl donor for DNA, RNA, proteins and lipids (3). In addition, folic acid and other B-complex vitamins have been proved to be important co-factors in pregnancy because it has been shown that they affect DNA methylation in children. In addition, maternal folic acid supplementation appears to protect against some childhood diseases, such as neural tube defects (4).

Childhood cancer, although rare, is a group of active and non-communicable diseases with a large number of unexplored data. Common types of cancer that occur in children include leukemia, neuroblastoma, lymphoma, Wilms's tumors, Hodgkin's disease, germ cell tumors, soft tissue sarcomas, retinoblastoma, and osteosarcoma. Leukemia appears to be the most commonly diagnosed childhood cancer, accounting for over 30% of all cases (5).According to a 2004 study, about 3,250 children under the age of 20 are diagnosed with leukemia each year, and about 2,400 cases are acute lymphoblastic leukemia (ALL) (6) - 80% of cases in children under 15 years of age appear to correspond to acute lymphoblastic leukemia (ALL), 17% to acute myelogenous leukemia (AML) and 3% to chronic myelogenous leukemia (6), (7). It is estimated that only 5-10% of cancers are due to a genetic mutation, while 90-95% appear to be due to lifestyle, infection and climate conditions. In this way, it is predicted that maternal diet is responsible for about 30-40% of cases (8), (9). A 2017 study in rodents confirmed that diet seems to have a greater impact on the development of cancer than the amount of carcinogen to which one is exposed, as food is made up of numerous substances and nutrients, each of which affects genes throughout the body and consequently many bodily functions (10). Initially, chromosomal shifts appear to be present at birth in children who later develop leukemia (11), (12), a factor that raises interest in the effect of prenatal exposure. Subsequently, birth weight has often been associated with an increased risk of ALL (13), especially in children <5 years of age (14), although zero results (15), (16) have been reported, which may indicate a quantitative or qualitative effect of mothers' nutrition during pregnancy (17). Dietary factors seem to be responsible for at least 30% of all types of cancer in developed countries (18). At this point, however, it would be important to note that most of the research that has been done, which mainly studied cases of leukemia, did not include cases of infantile leukemia, as the majority of these cases appear to have a specific genetic abnormality in chromosome zone 11q containing the MLL gene (19), (20).

MATERIAL AND METHOD

A variety of research data published worldwide from 2004 to 2017, in various countries, such as the USA and Greece, including meta-analyses and clinical studies, was studied in this literature review. . Many of the surveys included used the same or similar weighted questionnaires about food groups and were sometimes tailored to the needs/habits of each population and social group of participants.

So, a variety of food groups were studied and emphasis was placed on the results that represent the most commonly consumed food groups in the world.

Some food groups tested were fruits, vegetables, proteins, micronutrients from dietary sources and supplements (e.g. folic acid and vitamins), coffee and tea consumption (3), (4), (21). Foods were generally selected in the various surveys, representing a wide range of nutrients, including total calories, macronutrients, fiber, vitamins, minerals, antioxidants and micronutrients such as carotenoids and phytoestrogens. They also included processed meat products and vitamin supplements (multiple but also single vitamins) (6). The food groups, for example, surveyed in a 2005 study in Greece were cereals and starchy roots, sugars and syrups, legumes and nuts, vegetables, fruits, meat and meat products, fish and seafood, milk and dairy products and butter and margarine (22).

RESULTS

Research shows that pregnant women who follow a rich vegetable and fruit diet can help reduce the risk of childhood cancer. Research has shown that maternal intake of vegetables, fruits and protein sources is inversely related to childhood ALL. Consumption of carrots, beans or peas, melon and beef were the specific foods that were inversely associated with the disease. In a 2004 study by Jensen et al, in an analysis of the vegetable food group, the strongest inverse correlation of intake with ALL appeared for carrots and the fruit group. In the case of beef and legumes (which were considered non-expected elements), the antioxidant tripeptide glutathione, which is found in both meat and vegetable protein sources such as legumes, was considered to be a possible causal factor in this study and it was individually inversely associated with the disease. However, in this study, no correlation was found between consumption of broccoli, cauliflower, or Brussels sprouts and ALL risk. It has been shown, therefore, that increased maternal intake immediately before pregnancy (and, consequently, during it) of vegetables and fruits is associated with a reduced risk of ALL in offspring (6).

In a nationwide case study in Greece of children aged 12 to 59 months, it was found that the consumption of increased amounts of vegetables, fruits, fish and seafood by the mother during pregnancy is associated with a reduced risk of ALL in the offspring, while on the contrary increased consumption meat and meat products, sugars and syrups are associated with an increased risk of ALL in children. A marginal inverse correlation was also observed between maternal milk consumption and dairy products (22).

In a 2009 study by Kwan et al., six foods were found to be inversely related to the risk of ALL in children: carrots, melons, oranges, green beans, but also beans (fruit) and beef. This study, which had data from two phases (phase 1 and 2 from the NCCLS) found that the intake of vegetables, fruits, legumes and protein in the 12 months before pregnancy (and in conclusion and early pregnancy) is also related conversely with the risk of disease of the offspring. The results of this research generally agreed with those of the case study in Greece (Table 2). In contrast to research in Greece, however, the data here showed that the consumption of meat and meat products was associated with a moderate increase in the risk of disease (23).

In the case of processed meat, various research data seem to differ, with previous research showing, among other issues (with limited data at the time), a link between cold cuts as a potentially carcinogenic N-nitroso and childhood malignancies, including ALL (24) and subsequent research data to dispute the existence of this correlation regarding the occurrence of ALL (25), (26). In a 2004 study in the United States, the sausage team was extensively studied and it was found that the consumption of processed meat, hot dogs, sausages and bacon, lunches or whole meats by the mother were inversely associated with the disease, without statistically significant correlation. As the consumption of vitamins C and E has been shown by other studies to be able to inhibit nitration reactions and it has now been shown to prevent the formation of brain tumors in the offspring of pregnant animals fed N-nitroso precursors (27), Jensen et al., Examined in their research the interaction between the consumption of cold cuts and the intake of vitamins C and E (from diet and supplements). Consumption of these nutrients, however, did not appear to modify the risk of disease associated with the consumption of salted meat (6).

Subsequently, concerning caffeine consumption, it was found that there was an increased risk of developing ALL when mothers consumed more than four cups of coffee per day during pregnancy (28).

Caffeine consumption during pregnancy appears to be

associated with an increased risk of developing ALL, AML and the likelihood of an infant with leukemia, while others have failed to find a correlation, as summarized in a recent meta-analysis (28). However, there is some evidence from these studies that suggest that the increased risk of leukemia associated with maternal coffee consumption may be more pronounced in children born to non-smoking mothers (29).

Similarly, cola-based beverages have been associated with an increased risk of childhood ALL(30). It is worth noting that a general limitation of these studies is the lack of information on the type of beverages (eg caffeinated or not, green or black tea) that contain different nutrients and other compounds with anti-carcinogenic or precancerous properties (31)

On the micro-macro level, research has shown that exposure of the fetus to bioactive compounds (vitamins and minerals, fiber, peptides and amino acids) contained in vegetables, fruits and protein foods may contribute to reduce the risk of infant or childhood cancer (23). Fruits and vegetables contain vitamins and minerals that have been shown to have anti-cancer, anti-proliferative and anti-inflammatory effects. Their consumption reduces the occurrence of various types of cancer (Table 1).

Certain food groups, in particular, have been shown to reduce the risk of childhood leukemia. In fact, their consumption reduces more specifically the risk of developing infantile leukemia (32).

In particular, consumption of antioxidant micronutrients, such as provitamin A carotenoids, A carotene and B carotene, has been shown to be inversely related to the risk of ALL, as they may protect against oxidative damage to biomolecules such as lipids and DNA and therefore affect the risk of developing cancer. The prevention of DNA damage and the improved repair of DNA, in fact with supplements with fruits, juices and several carotenoids, has emerged from a wealth of research data (33), (34), (35), (36), (37). These data were also verified in a 2009 study, where maternal consumption of provitamin A carotenoids (found in fruits and vegetables) (AOR 50.77, 95% CI 0.60.0.98), and reduced glutathione consumption (found in protein contained in food) (AOR 50.49, 95% CI 0.27, 0.90) were inversely related to the risk of ALL (23).

Glutathione is an important physiological antioxidant that works in the synthesis and repair of DNA and plays a critical role in the detoxification of harmful compounds and the recycling of vitamins C and E in their reduced forms (6). The antioxidant glutathione tripeptide, found in both meat and vegetable protein sources such as legumes, appears to be individually inversely related to ALL (6), (23).

Vitamin intake and absorption during pregnancy appear to have a greater impact on the infant's vitamin reserves than on the mother's reserves (5). Vitamin B12 deficiency is one of the most common micronutrient deficiencies in pregnant women (38). Infants with B12 deficiency are then thought to be at risk of developing several neurological, hematological and developmental defects (39).

About iron and calcium, no specific association has been found with childhood cancer; however, studies highlight the importance of iron and calcium supplements to the pregnant woman to protect the mother herself (40). Research has also shown that catechins and quercetin (substances found in tea) are involved in leukemogenesis (22).

In addition, data from time to time have correlated fetal morphological development with fetal folic acid uptake and carbon metabolism (41), (42). In fact, daily folic acid supplementation of 400–800 lg is recommended for all women of childbearing potential, in order to reduce the risk of neural tube defects (NTD) in the offspring, from two months before to three months after conception (22). Maternal prevention of folic acid and other nutrients involved in carbon metabolism appears to affect the risk of childhood leukemia due to the importance of these nutrients to DNA (32). Folic acid, as a critical cofactor involved in DNA synthesis, is required for cell division and growth, thus explaining the use of antiplatelet drugs in cancer chemotherapy. This raises the question of whether taking folic acid supplements and therefore possibly the increased amount, could ultimately lead to increased risks of carcinogenesis (40). Descendants of women who took folic acid supplements (found naturally in many leafy vegetables) during pregnancy appeared to have a lower risk of ALL (43).

Finally, as for folic acid and Vitamin D, a study conducted in 2004 did not provide evidence of a significant reduction in the risk of ALL associated with maternal intake (through dietary supplements), before pregnancy, or with the consumption of any type. supplement, including those containing vitamin C (6).

In order to further investigate the above data, data were also sought on the dietary supplements received by the pregnant woman and their possible association

with the risk of cancer in the offspring. The nutritional status of the mother before pregnancy and the observance of nutritional supplements, along with the sex of the fetus, seem to be important factors that influence the way how supplements affect the outcome of the pregnancy and the survival success of the newborn (44).

Although the change in caloric and macronutrient requirements during pregnancy appears to be small, the need for micronutrients increases exponentially during pregnancy, especially for essential elements such as iron, folic acid, iodine, calcium and vitamin D (45). Previous studies have shown that maternal supplementation containing folic acid, with or without iron, and cod liver oil, containing vitamins A and D, is associated with a reduced risk of ALL in childhood (46). Nevertheless, in the studies, the regular use of any dietary supplement did not appear to be associated with disease risk (22), (23).

In a US study conducted in 2004, the food frequency questionnaires used included questions about the use of multiple vitamin supplements, multiple antioxidant supplements, and individual supplements containing vitamin A, B-carotene, vitamin C, zinc and selenium. Thus, the reception of each element was studied individually, as well as a multi-supplement. Consumption of individual micronutrients by supplements alone did not appear to be associated with ALL. The odds ratios were all close to 1.0 (ranging from 0.89 to 1.00) and none were statistically significant (6).

Discussion:

At this point, however, it would be important to pay particular attention to the limitations of the various studies which may have influenced the research data. An important issue that emerges is the recall bias, as most surveys use self-report questionnaires and therefore, there is an increased chance that a measurement error will occur, but also that nutritional factors are incorrectly correlated with each other by the participants in these surveys (23). Thus, care is required in the immediate attribution of risk or benefit to any particular food or nutrient. In addition, the sample size may be a limitation, especially for a heterogeneous disease, such as childhood ALL, which probably has a different etiology depending on the age of diagnosis (6).

Nevertheless, it is important to take into account the advantages of the studied publications. Most studies were performed on individually matched pairs of ALL cases of different ages that had been diagnosed over time and the questionnaires used covered a variety of food groups and micronutrients.

In addition, they covered socio-demographic variables and an extensive section assessing maternal nutritional intake, including standard portion sizes, during pregnancy, limiting the effect of confounding factors and often taking care of their weighting (28).

As further food for thought, a meta-analysis must be carried out - a systematic review of all foods and not only supplements, in the present possible studies, but also newer ones, in order to make full use of all possible data that could offer these surveys. It is also necessary to investigate further, as far as possible, infant cancer in relation to the mother's diet, as well as the possible association of a gene mutation with the pregnant woman's diet through possible DNA methylation, as the data in this sector seems to be deficient. In conclusion, it would be interesting to further investigate the inverse association of dietary glutathione with cancer risk observed in some studies (6).

References

1. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean Diet and Survival in a Greek Population. New England Journal of Medicine. 2003;348(26).
2. Luyckx V, Perico N, Somaschini M, Manfellotto D, Valensise H, Cetin I, et al. A developmental approach to the prevention of hypertension and kidney disease: a report from the Low Birth Weight and Nephron Number Working Group. Vol. 390, The Lancet. 2017.
3. Locasale JW. Serine, glycine and one-carbon units: Cancer metabolism in full circle. Vol. 13, Nature Reviews Cancer. 2013.
4. Lim U, Song MA. Dietary and lifestyle factors of DNA methylation. Vol. 863, Methods in Molecular Biology. 2012.
5. Wisehart Lindsay. Health Effects of a Vegan Diet and Pediatric Cancer Prevention. 2019.
6. Jensen CD, Block G, Buffler P, Ma X, Selvin S, Month S. Maternal Dietary Risk Factors in Childhood Acute Lymphoblastic Leukemia (United States). Cancer Causes & Control 2004 15:6 [Internet]. 2004 Aug [cited 2022 Apr 10];15(6):559–70. Available from: https://link.springer.com/article/10.1023/B:CACO.0000036161.98734.17
7. Parkin DM, Stiller CA, Draper GJ, Bieber CA. The international incidence of childhood cancer. International Journal of Cancer. 1988;42(4).
8. Davoodi H, Esmaeili S, Mortazavian AM. Effects of milk and milk products consumption on cancer: A review. Comprehensive Reviews in Food Science and Food Safety. 2013;12(3).
9. O'Neill B. A scientific review of the reported effects of vegan nutrition on the occurrence and prevalence of cancer and cardiovascular disease. Vol. 3, Bioscience Horizons. 2010.
10. Campbell TC. Cancer Prevention and Treatment by Wholistic Nutrition. J Nat Sci. 2017;3(10).
11. Gale KB, Ford AM, Repp R, Borkhardt A, Keller C, Eden OB, et al. Backtracking leukemia to birth: Identification of clonotypic gene fusion sequences in neonatal blood spots. Proc Natl Acad Sci U S A. 1997;94(25).
12. Hjalgrim LL, Madsen HO, Melbye M, Jørgensen P, Christiansen M, Andersen MT, et al. Presence of clone-specific markers at birth in children with acute lymphoblastic leukaemia. British Journal of Cancer. 2002;87(9).
13. Cnattingius S, Ekbom A, Adami HO, Zack M, Gunnarskog J, Linet M, et al. Prenatal and Neonatal Risk Factors for Childhood Myeloid Leukemia. Cancer Epidemiology Biomarkers and Prevention. 1995;4(5).
14. Okcu MF, Goodman KJ, Carozza SE, Weiss NS, Burau KD, Bleyer WA, et al. Birth weight, ethnicity, and occurrence of cancer in children: A population-based, incident case-control study in the State of Texas, USA. Cancer Causes and Control. 2002;13(7).
15. Kaye SA, Robison LL, Smithson WA, Gunderson P, King FL, Neglia JP. Maternal reproductive history and birth characteristics in childhood acute lymphoblastic leukemia. Cancer. 1991;68(6).
16. Savitz DA, Ananth C v. Birth characteristics of childhood cancer cases, controls, and their siblings. Pediatric Hematology and Oncology. 1994;11(6).
17. Lagiou P, Mucci L, Tamimi R, Kuper H, Lagiou A, Hsieh CC, et al. Micronutrient intake during pregnancy in relation to birth size. European Journal of Nutrition. 2005;44(1).
18. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab. 2014 Mar;99(3):923-31. doi: 10.1210/jc.2013-2409. Epub 2014 Jan 1. PMID: 24423323.
19. Cortes JE, Kantarjian HM. Acute lymphoblastic leukemia a comprehensive review with emphasis on biology and therapy. Vol. 76, Cancer. 1995.
20. Ernst P, Wang J, Korsmeyer SJ. The role of MLL in hematopoiesis and leukemia. Vol. 9, Current Opinion in Hematology. 2002.
21. Vollset SE, Clarke R, Lewington S, Ebbing M, Halsey J, Lonn E, et al. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet [Internet]. 2013 [cited 2022 Apr 10];381(9871):1029–36. Available from: https://pubmed.ncbi.nlm.nih.gov/23352552/
22. Petridou E, Ntouvelis E, Dessypris N, Terzidis A, Trichopoulos D, Moschovi M, et al. Maternal diet and acute lymphoblastic leukemia in young children. Cancer Epidemiology Biomarkers and Prevention. 2005;14(8).
23. Kwan ML, Jensen CD, Block G, Hudes ML, Chu LW, Buffler PA. Maternal diet and risk of childhood acute lymphoblastic leukemia. Public Health Reports. 2009;124(4).
24. Blot WJ, Henderson BE, Boice JD. Childhood cancer in relation to cured meat intake: Review of the epidemiological evidence. Vol. 34, Nutrition and Cancer. 1999.
25. Ross JA, Potter JD, Reaman GH, Pendergrass TW, Robison LL. Maternal exposure to potential inhibitors of DNA topoisomerase II and infant leukemia (United States): Report from the Children's cancer group. Cancer Causes and Control. 1996;7(6).
26. Sarasua S, Savitz DA. Cured and broiled meat consumption in relation to childhood cancer: Denver, Colorado (United States). Cancer Causes & Control. 1994;5(2).
27. Ivankovic S, Preussmann R, Schmaehl D, Zeller JW. Prevention by ascorbic acid of in vivo formation of N nitroso compounds. IARC (International Agency for Research on Cancer) Scientific Publications. 1974;vol 9.
28. Menegaux F, Steffen C, Bellec S, Baruchel A, Lescoeur B, Leverger G, et al. Maternal coffee and alcohol consumption during pregnancy, parental smoking and risk of childhood acute leukaemia. Cancer Detection and Prevention. 2005;29(6).
29. Bonaventure A, Rudant J, Goujon-Bellec S, Orsi L, Leverger G, Baruchel A, et al. Childhood acute leukemia, maternal beverage intake during pregnancy, and metabolic polymorphisms. Cancer Causes and Control. 2013;24(4).
30. Thomopoulos TP, Ntouvelis E, Diamantaras AA, Tzanoudaki M, Baka M, Hatzipantelis E, et al. Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: A meta-analysis. Vol. 39, Cancer Epidemiology. 2015.
31. Milne E, Royle JA, Bennett LC, de Klerk NH, Bailey HD, Bower C, et al. Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: Results from an Australian case-control study. Cancer Causes and Control. 2011;22(2).

32. Spector LG, Xie Y, Robison LL, Heerema NA, Hilden JM, Lange B, Felix CA, DaviesSM, Slavin J, Potter JD, Blair CK, Reaman GH, Ross JA (Maternal diet and infant leukemia: the DNA topoisomerase II inhibitor) Cancer Epidemiol Biomarkers Prev. 2015 Mar; 14(3):651-5
33. Astley SB, Elliott RM, Archer DB, Southon S. Increased cellular carotenoid levels reduce the persistence of DNA single-strand breaks after oxidative challenge. Nutrition and Cancer. 2002;43(2).
34. Collins AR, Harrington V, Drew J, Melvin R. Nutritional modulation of DNA repair in a human intervention study. Carcinogenesis. 2003;24(3).
35. Fillion L, Collins A, Southon S. Beta-carotene enhances the recovery of lymphocytes from oxidative DNA . Acta BiochimicaPolonica . 1998;183–90.
36. Torbergsen AC, Collins AR. Recovery of human lymphocytes from oxidative DNA damage; the apparent enhancement of DNA repair by carotenoids is probably simply an antioxidant effect. European Journal of Nutrition. 2000;39(2).
37. Wolterbeek APM, Roggeband R, van Moorsel CJA, Baan RA, Koeman JH, Feron VJ, et al. Vitamin A and β-carotene influence the level of benzo[a]pyrene-induced DNA adducts and DNA-repair activities in hamster tracheal epithelium in organ culture. Cancer Letters. 1995 May;91(2):205–14.
38. Piccoli GB, Clari R, Vigotti FN, Leone F, Attini R, Cabiddu G, et al. Vegan-vegetarian diets in pregnancy: Danger or panacea? A systematic narrative review. Vol. 122, BJOG: An International Journal of Obstetrics and Gynaecology. 2015.
39. Pawlak R. To vegan or not to vegan when pregnant, lactating or feeding young children. Vol. 71, European Journal of Clinical Nutrition. 2017.
40. Parisi F, di Bartolo I, Savasi VM, Cetin I. Micronutrient supplementation in pregnancy: Who, what and how much? Vol. 12, Obstetric Medicine. 2019
41. Cetin I, Berti C, Calabrese S. Role of micronutrients in the periconceptional period. Vol. 16, Human Reproduction Update. 2009.
42. Fekete K, Berti C, Cetin I, Hermoso M, Koletzko B v., Decsi T. Perinatal folate supply: Relevance in health outcome parameters. Maternal and Child Nutrition. 2010;6(SUPPL. 2).
43. Thompson JR, Gerald PF, Willoughby MLN, Armstrong BK. Maternal folate supplementation in pregnancy and protection against acute lymphoblastic leukaemia in childhood: A case-control study. Lancet. 2001;358(9297).
44. Smith ER, Shankar AH, Wu LSF, Aboud S, Adu-Afarwuah S, Ali H, et al. Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries. The Lancet Global Health. 2017;5(11).
45. King JC. Physiology of pregnancy and nutrient metabolism. In: American Journal of Clinical Nutrition. 2000
46. Shu XO, Gao YT, Tu JT, Zheng W, Brinton LA, Linet MS, et al. A population-based case-control study of childhood leukemia in shanghai. Cancer. 1988;62(3).