Impact of maternal dietary lipids on human health

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Abstract – During the perinatal period, maternal dietary polyunsaturated fatty acids (PUFA) ensure optimal infant development. Observational studies on cognitive and visual development reported that a specific deficit intake in n-3 PUFA in pregnant women was associated with a reduction in visual acuity in 2-months-old infants. Moreover, a low docosahexaenoic acid (DHA) content associated with a high level of n-6 PUFA in breast milk was negatively associated with the degree of cognitive development in 6-years-old children. As regards to adipose tissue development, only observational human data agree with the hypothesis that excessive dietary intakes of n-6 PUFA compared with n-3 PUFA could promote the development of adipose tissue and obesity. With regard to immune system development, observational and clinical studies suggest that long-chain n-3 PUFA consumption during pregnancy may prevent the incidence of allergic diseases in children. Lastly, specific association between the maternal ingestion of food groups and the infant health has been studied mainly on allergic outcomes (fish, dairy products). Nutritional recommendations for PUFA intake in pregnant and lactating women were mainly based on brain development data, corresponding to breast milk levels of 10% of total fatty acids for linoleic acid, 1.5% for α-linolenic acid and 0.4% for DHA.

Keywords: allergic diseases / dairy products / breast milk / brain development / maternal nutrition / obesity / polyunsaturated fatty acids (PUFA)

Résumé – Nutrition lipidique périnatale et santé de l’Homme. L’apport en acides gras polyinsaturés (AGPI) de l’alimentation maternelle participe au développement optimal du nourrisson et de l’enfant. Les études d’observation rapportent qu’un déficit spécifique d’apport alimentaire en AGPI n-3 pendant la grossesse est associé à une réduction du niveau d’acuité visuelle chez l’enfant à l’âge de 2 mois, et que le développement cognitif des enfants à l’âge de 6 ans est associé négativement avec une teneur faible en AGPI n-3 et élevée en AGPI n-6 dans le lait maternel. Elles montrent également qu’un déséquilibre du métabolisme maternel des AGPI en faveur de celui de la série n-6 par rapport aux n-3, favorise le développement du tissu adipeux et de l’obésité chez le jeune. Pour le développement du système immunitaire, les études d’observation et cliniques suggèrent que la consommation d’AGPI n-3 à longue chaîne pendant la grossesse peut prévenir l’incidence des maladies allergiques de l’enfant. Des données sont également disponibles concernant des classes d’aliments (poisson, produits laitiers) et l’incidence des manifestations allergiques. Les recommandations nutritionnelles destinées à la femme enceinte et allaitante s’appuient sur les données du développement cérébral, et correspondent dans le lait maternel à des teneurs d’environ 10 % des acides gras totaux pour l’acide linoléique, 1,5 % pour l’acide α-linolénique et 0,4 % pour le DHA.

Mots clés : acides gras polyinsaturés (AGPI) / développement cérébral / lait maternel / nutrition maternelle / maladies allergiques / obésité / produits laitiers

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1 Introduction

During the perinatal period of development, lipids of the maternal diet are of great importance since they exert significant effects on the development of the fetus and the infant, involving the cerebral and visual functions (Guesnet et al., 2013), but also on the incidence of inflammatory pathologies in infant and child (asthma, allergic diseases) (Miles and Calder, 2017). In the longer term, they may be at the origin of metabolic disturbances that will perpetuate throughout life, favoring in children and adults the emergence of pathologies such as obesity and its associated metabolic complications (Koletzko, 2016). Human studies in neonatal nutrition were conducted in order to determine the impact of maternal fatty acid dietary intake during pregnancy and lactation. The aim of this review is to provide a quick overview of the knowledge gained about the impact of maternal lipid nutrition during pregnancy and lactation, and more specifically of n-6 and n-3 polyunsaturated fatty acids (PUFA) on the fatty acid levels in maternal and infant blood and plasma lipids, as well as on the fatty acid composition of breast milk, and on the development and health of infants and children. Moreover, specific association between the maternal ingestion of food groups and the infant health is presented in order to evaluate the impact of maternal fish and dairy fat consumption on allergic outcomes, fish being the main source of dietary long-chain n-3 PUFA and dairy fats a primary source of dietary lipids consumed in occidental population.

2 Maternal PUFA intake and PUFA levels in mother and infant blood, and in human milk

Five major PUFA exert crucial biological functions in humans during the perinatal period of active cellular membrane development taking place from the later part of pregnancy until the early infancy: linoleic acid (LA, 18:2n-6) and α-linolenic acid (ALA, 18:3n-3), the respective precursors of the n-6 and n-3 series, and three long-chain (LC) derivatives, arachidonic acid for the n-6 series (AA, 20:4n-6), and eicosapentaenoic (EPA, 20:5n-3) and docosahexaenoic (DHA, 22:6n-3) acids for the n-3 series. During pregnancy, they are transported from maternal circulation to the fetus across the placenta, but LC-PUFA such as AA and DHA are more selectively and actively transferred than PUFA precursors as evidenced by their higher levels in the fetus than in the maternal plasma (Crawford et al., 1981). Therefore, increasing the maternal dietary intake of DHA during the last trimester of pregnancy allows to elevate the DHA content in maternal plasma and red blood cells and consequently the DHA status of the developing fetus (concentration in cord blood) (Connor et al., 1996) (Fig. 1). In contrast, maternal dietary intake of ALA is less efficient to elevate the DHA status of the fetus due to low maternal conversion of ALA to DHA. During lactation, both dietary LC-PUFA and PUFA precursors are transferred into breast milk lipids. Breast milk PUFA are also derived from their mobilization from adipose tissues which have been partly constituted before and during pregnancy. Furthermore, it has been shown that LA milk content is more closely correlated to that of the adipose tissue than that of the maternal diet (Martin et al., 1993): two-thirds derivate from mobilization of adipose tissue and one-third directly from the maternal diet. Therefore, PUFA concentrations are highly dependent on maternal intakes during both pregnancy and lactation periods. The LA content of human milk varies from a factor of 1 to 6 and can reach for about 30% of total fatty acids in USA (Ailhaud et al., 2006) (Fig. 2, Part A), and more than 30% in strict vegetarian women consuming no animal products (Sanders et al., 1978; Burdge et al., 2017). In Western countries during the last 50 years, LA mean content has significantly increased in human milk due to specific marked changes in the nature of lipid consumed, and notably in USA ranging from less than 5% of total fatty acids in the 1950s to more than 15–25% today (Ailhaud et al., 2006) (Fig. 2, Part A). With regard to n-3 PUFA, variations are even more marked since ALA and DHA contents vary respectively from 0.5 up to 6% in women supplemented with linseed oil, and from <0.1% to more than 1.5% in women supplemented with fish oil (Gibson et al., 1997) or in populations consuming large amount of seafood (Innis and Kuhnlein, 1988) (Fig. 2, Part A). Today in France, LA averages 10% of total fatty acids in human milk and ALA 0.9%, ending with a ratio LA/ALA close to 12 (Mazurier et al., 2017). Two-thirds of long-chain n-3 PUFA are in the form of docosahexaenoic acid (22: 6n-3, DHA), which represents 0.2–0.3% of total fatty acids.

Lastly, human milk contains high concentrations of saturated fatty acids (SFA, 50% of total fatty acids) mainly as the form of palmitic acid (16:0, 23%), myristic acid (14:0, 8%) and medium chain fatty acids (8:0–12:0, 9%) (Guesnet et al., 2013). It also contains high levels of monounsaturated fatty acids (MUFA), accounting for about 40% of total fatty acids, mostly as oleic acid (18:1n-9, 34%). Milk levels of SFA and MUFA are also modified by maternal dietary intake but to a lesser extent than PUFA. Nevertheless, SFA and palmitic acid levels can be reduced by half in the milk of vegetarian women consuming little saturated animal fats. The impact of such specific decrease in milk palmitic acid on the child’s health is unknown. This fatty acid is involved in many crucial functions and it might be essential during development (Innis, 2016). LA concentration in human milk could be significantly decreased in lactating women consuming high amounts of

![Fig. 1. Impact of DHA supplementatio](image-url)
saturated animal fats (such as butter and dairy fats) compared to women with high consumption of vegetable oils (Yahvah et al., 2015).

3 Maternal PUFA intake: infant cognitive and visual development

DHA is highly concentrated in cerebral and retinal membranes since it takes account for about 25% of total fatty acids in the human cerebral cortex and more than 30% in the whole retina. The accretion of DHA in human brain phospholipids occurs primarily during the fetal brain growth spurt of active neurogenesis and cell maturation (i.e., the last trimester of pregnancy), and the early postnatal period of development of intense synaptogenesis (first two years of life) (Alessandri et al., 2004). Animal models of chronic dietary n-3 PUFA deficiency applied during all the period of pregnancy and lactation induce in the young a marked decline of the incorporation of DHA in brain and retina membranes, and significant alterations in behavioral performances and learning and visual functions which persist in adulthood (Alessandri et al., 2004). Restoration of normal brain DHA contents after the period of development is possible by fish oil feeding, but some alterations in visual parameters remain abnormal (Anderson et al., 2005). In agreement with these animal data, clinical studies conducted in term infants fed with low n-3 PUFA formulas have reported significant decrease in brain DHA concentration and alterations in visual acuity at 4 months and 3 years of age (Farquharson et al., 1995; Uauy et al., 2001).

For the infant brain and retina development, most of the human studies have been focused on PUFA and more specifically on n-3 LC-PUFA. With regard to the pregnancy period, several observational and clinical studies have specifically evaluated the association of maternal n-3 PUFA status and dietary intake with the infant neurodevelopment outcomes. Epidemiological data measuring blood DHA concentrations in women at the end of pregnancy and in infants at birth (cord) have generally reported positive associations between DHA status, and cognitive and visual functioning in infants aged from 2 days to 7 years (reviewed in Gould et al., 2016). Randomized controlled trials have mainly investigated the effect of DHA supplementation during the last half of pregnancy on infant and child cognitive and visual development from several months of age until the age of 12 years. They reported controversial results due to several experimental limitations such as too small numbers of enrolled mothers and their infants (<100) and uncontrolled potential biases (reviewed in Gould et al., 2016). One large randomized controlled trial was conducted on 2399 pregnant women...
receiving a dietary supplement of 800 mg DHA/day until delivery, and their children were followed from birth until the age of 7 years (the DOMInO trial) (Gould et al., 2016). Globally, data from this trial did not show clear effects of DHA supplementation during pregnancy on neurodevelopmental outcomes in 18-months-old infants and on general cognitive functioning in 4-years-old children. However, 4-years-old children whose mothers received the DHA supplement had lower mild delayed cognitive development.

In all these studies, it was hypothesized that the studied populations of pregnant women consumed typical Western diets high in n-6 PUFA and low in n-3 PUFA. However, no PUFA maternal dietary intakes were assessed before DHA supplementation, women who consumed non-adequate intakes of n-3 PUFA not being distinguished from women consuming adequate intakes. In other series of observational and clinical studies conducted in Canada (Innis and Elias, 2003; Innis and Friesen, 2008; Mulder et al., 2014), daily usual intakes of individual n-6 and n-3 PUFA were quantified in pregnant women and then validated by the measurement of PUFA levels in plasma phospholipids (Innis and Elias, 2003). During the last trimester of pregnancy, 40% were considered as DHA-deficient since they consumed a quantity of DHA lower than the total amount deposited in the fetus during this period (Innis and Friesen, 2008). Moreover, the DHA deficiency was amplified in some pregnant women because their ALA dietary intake was low and associated with a high LA/ALA ratio unfavorable for the DHA synthesis. Clinical data showed an increased risk of lower visual acuity in 2-months-old infants and of lower DHA synthesis. Clinical data showed an increased risk of lower visual acuity in 2-months-old infants and of lower DHA amounts in their red blood cell and in infants whose mothers consumed these unbalanced diets, in comparison to infants whose mothers have received a DHA supplementation (400 mg/d) until delivery (Innis and Friesen, 2008; Mulder et al., 2014).

4 Maternal PUFA intake, obesity and allergic diseases

4.1 Obesity

Adipose tissue development in humans is particularly active during the perinatal period. It involves an increase of both number (differentiation and proliferation) and size (hypertrophy) of adipocytes, and it is sensitive to lipid nutrition. Based on in vitro and in vivo animal studies, it has been hypothesized that a disequilibrium of PUFA metabolism in favor of the n-6 series (due to imbalance of maternal dietary intakes of PUFA precursors [LA/ALA ratio] and of their major long-chain [AA/EPA+DHA ratio]), could increase the risk of excessive adipose tissue development and might be an important parameter for the increased prevalence of overweight and obesity in children and adults in Western countries (Ailhaud et al., 2006; Ailhaud et al., 2008). Indeed, in rodent models, high LA/ALA ratio (> 25) in the maternal diet increased the fat mass at weaning until adulthood (Massiera et al., 2003). It also raised tissue and milk contents of arachidonic acid while decreasing EPA and DHA, which in turn increased prostacyclin production and then the signaling pathways favoring adipogenesis. Balancing the LA/LNA dietary ratio by a reduction to value of 2 suppresses both the increased fat mass and n-6 PUFA levels in tissues and milk. Lastly, data on high dietary intakes of EPA and DHA during the entire period of growth suggested an inhibitory effect on adipose tissue development in young and adult rodents, though data were inconsistent when EPA-DHA supplementation was strictly achieved during the perinatal period (pregnancy-lactation) (Hauner et al., 2013).

In humans, several observational studies conducted on a large number of mother-child pairs have reported that adiposity in children at 3 to 6 years of age was positively correlated with LA and n-6 PUFA levels and the AA/EPA+DHA ratio in maternal plasma during pregnancy (third trimester), and with the AA/EPA+DHA ratio in their blood at birth (cord) (Donahue et al., 2011; Moon et al., 2013; Bernard et al., 2017b). In the Generation R study, similar results were observed in maternal n-3 and n-6 PUFA concentrations in plasma at mid-pregnancy for total body fat mass and preperitoneal fat in infants at 6 years of age (Vidakovic et al., 2016). With regards to the period of lactation, only few studies have investigated the relation between breast milk PUFA concentrations and the development of adiposity in children who were breastfed. Similar trends were observed, such as a significant increase in body fat mass in 4-months-old breastfed infants whose mother’s milk has high ratio of AA/EPA+DHA (Rudolph et al., 2017), and a negative association between milk DHA content and the fat mass in infants aged from 2 to 7 years (Pedersen et al., 2012). Lastly, few randomized controlled trials have been conducted during pregnancy and/or lactation and exclusively by supplementing the maternal diet with long-chain n-3 PUFA between 0.2 to 1.2 g/d (reviewed in Hauner et al., 2013). Results on infant body composition are inconsistent because the timing and duration of the PUFA supplementation were quite variable among studies and no data on maternal fatty acid intake at baseline were reported, which does not allow to determine a possible PUFA disequilibrium in these populations of women.
4.2 Allergic diseases

The development of the immune system takes place during the pre- and post-natal periods of development in humans and is modulated by the maternal nutrition. It is admitted that a high ratio of n-6/n-3 PUFA exerts negative effect on immune cell functioning and inflammation, and therefore on the risk of allergic diseases. This effect involved notably the increased production of pro-inflammatory eicosanoids derived from n-6 PUFA (AA), at the expense of anti-inflammatory pro-resolving mediators produced from n-3 long-chain PUFA (EPA and DHA) (Miles and Calder, 2017). As regards to pregnancy, observational studies have suggested a protective association of the consumption of n-3 long-chain PUFA by the mothers on the risk of allergic manifestations in infants and children, but globally results are not clear (Miles and Calder, 2017). Randomized controlled trials supplementing the diet of pregnant women with fish oil at high doses of EPA+DHA (from 0.9 g/d to 3.7 g/d) reported more convincing protective impact on asthma and atopic dermatitis in the young infant. Indeed, the supplementation of the pregnant women diet with 2.4 g/d EPA+DHA from the 24th week of pregnancy until the delivery was associated with a 30% decrease of the risk of asthma in infants until 5-years-old (Bisgaard et al., 2016). Regarding the period of lactation, the association with long-chain n-3 PUFA and/or fish consumption with the incidence of allergic diseases is not clearly established both for families at risk of allergies and those that are not at risk (Netting et al., 2014). However, the results are more convincing in youngest infants. Thus, in a study conducted on one hundred mother-infant pairs aged 6 to 12 months, an association was observed with the PUFA content of breast milk, which was positive with the incidence of asthma-like symptoms when mother’s breast milk contained high level of n-6 PUFA, and negative with the incidence of atopic diseases for high n-3 PUFA level (Soto-Ramirez et al., 2012).

5 Maternal consumption of dairy fats and infant health

Numerous epidemiological studies have been conducted to determine whether dietary patterns (Mediterranean diet, for example) or the ingestion of specific food groups by the mother during pregnancy and lactation were associated with health outcomes in infant, and notably allergy and atopic diseases (reviewed in Netting et al., 2014). Globally, there is no consistent association between maternal nutrition during either pregnancy or breastfeeding and the incidence of these diseases (Netting et al., 2014). For example, observational study data suggested a protective effect of the maternal fish consumption during either pregnancy via its high content of long-chain n-3 PUFA, but results lack of consistency. As regards to the consumption of dairy food products and of dairy lipids and the period of pregnancy, 3 observational studies reported semi-quantitative data on the maternal consumption of both butter, milk and milk products, and individual fatty acids (Lumia et al., 2011; Nwaru et al., 2012; Tuokkola et al., 2016). Despite large variations in the levels of consumption of dairy fats and fatty acids by the mother (butter: from 4 to 20 g/d; milk and milk derivatives: from 550 g to 1100 g/d), results were inconclusive for an effect on the risk of allergy and atopic diseases in infants, whereas a protective effect was noted for cow’s milk allergy (Tuokkola et al., 2016). The study of the consequences of dairy food products and dairy lipid consumption by the lactating woman have been exclusively focused on the incidence of atopic diseases (Thijs et al., 2011; Lumia et al., 2012) and one study has investigated the relation with the fatty acid concentration in human milk (Thijs et al., 2011). First, compared to a population of lactating women that rarely consumed dairy fats, the daily consumption of 4 dairy products + butter reduced significantly the breast milk contents of LA and ALA, without modifying their relative proportion (LA/ALA ratio). It also significantly increased saturated fatty acid contents as well as levels of fatty acid markers of dairy fats (vaccenic and rumenic acids). Only the study of Thijs et al. (2011), conducted on 310 mother-infant pairs, has reported a significant protective effect of dairy food consumption since the concentration of vaccenic and rumenic acids in women’s milk was negatively associated with the incidence of eczema and atopic dermatosis in 2-years-old infants. Moreover, a high breast milk content of long-chain n-3 PUFA was also predictive of a lower prevalence of these two diseases. Since dairy fats are low in LA, the protective effect of a high dairy food consumption could result in a rebalancing of the ratio of n-6 to n-3 PUFA by reducing the high LA maternal intake consequently to a decreased consumption of LA-rich margarines and vegetable oils (Jonsson et al., 2016).

6 Conclusions

Animal and human observational studies have well demonstrated that n-3 PUFA and DHA in the maternal diet are critically important for the development of cognition and vision of infants. However, randomized controlled trials using DHA supplementation have reported controversial data which could result from uncontrolled confounding factors. Among them, large variations between infants in their own potential of development were evidenced for visual acuity at the age of 2 months (Innis and Friesen, 2008). As regards to obesity and allergy diseases, further observational and clinical studies are needed to verify:

– whether a high maternal n-6 to n-3 ratio (diet, breast milk), due to a non-adequate low consumption of n-3 PUFA associated or not with a high LA consumption, could promote the prevalence of obesity and/or allergy diseases in infants and children;
– whether a prevention could be possible by a maternal dietary n-3 PUFA supplementation or by changing food dietary patterns in pregnant and lactating women to rebalance the ratio of n-6 to n-3 PUFA.

Thus, further human observational studies on fish and dairy fat consumption using precise quantitative data would help clarifying the effects of these foods during the perinatal period. This is of importance since most of current human diets in the Western industrialized world are generally low in n-3 PUFA, mainly as the form of long-chain EPA and DHA (Sioen et al., 2017), with some of them which are also high in LA as evidenced in USA (Ailhaud et al., 2006).
Meanwhile, specific recommended dietary intakes (RDIs) for PUFA have been published for women during pregnancy and lactation. The French Agency for Food, Environmental and Occupational Health & Safety recommended for pregnant and lactating women 4.6 g/d LA and 1.8 g/d ALA and 5.0 g/d LA and 2.0 g/d LA, respectively, and a RDI of 250 mg/d for DHA (ANSES, 2011). These guidelines would allow to reach about 10% of total breast milk fatty acids for LA, 1.5% for ALA and 0.4% for DHA (Fig. 2, Part B).

**In Memoriam**

In Memoriam of Dr. Sheila Innis (University Of British Columbia Department Of Paediatrics, Vancouver, Canada) who was a pioneer researcher in the field of n-3 PUFA and brain development, and conducted many clinical studies relating maternal diet to placental and breast milk fat transfer, as well as the impact of diet in child development and health (http://goedomega3.com/index.php/the-goed-current-editors-in-memoriam-of-dr-sheila-innis).

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