Editorial

See corresponding articles on pages 1472 and 1489.

Can long-chain PUFA supplementation during pregnancy influence later obesity risk?

*Michelle L Blumfield**

Department of Nutrition and Dietetics, School of Clinical Sciences, Faculty of Medicine, Nursing, and Health Sciences, Monash University, Clayton, Victoria, Australia

Epigenetic regulation of adipose tissue by maternal diet during pregnancy could be the next primary prevention strategy to reduce obesity (1). It is well known that human phenotype can be influenced by maternal stimulus during critical windows of fetal and early postnatal development. Offspring body composition may be modifiable by nutritional intervention in the mother, particularly regimens that focus on balancing macronutrient intakes. One approach that has gained considerable interest is the influence of maternal long-chain PUFAs (LCPUFAs)[1] during pregnancy on offspring adiposity. Several reviews on this topic have been published (2–6). Experimental studies provide biological plausibility for a role of LCPUFAs in early adipose tissue development (6). However, human studies are inconclusive and have produced mixed results (2). Therefore, high-quality randomized controlled trials (RCTs) are urgently required to establish whether n–3 LCPUFA supplementation during pregnancy affects offspring adiposity.

In this issue of the Journal, Muhlhausler et al. (7) and Brei et al. (8) present findings from 2 RCTs that provided no evidence to support the use of maternal n–3 LCPUFA supplementation during pregnancy as a preventative strategy against childhood obesity up to 5 y. In the study by Muhlhausler et al., women at <21 wk of gestation were recruited to an Australian multicenter, double-blind RCT (7). The aim of the study was to test the effects of daily DHA-rich fish-oil (800 mg DHA and 100 mg EPA/d) capsules during the second half of pregnancy on child BMI *z* score and percentage of body fat at 3 and 5 y. This study is novel because it represents the largest RCT of DHA supplementation during pregnancy ($n = 1531$) and reported high retention rates (92.2%) of children at both 3 and 5 y. The study included 2 measures of body fat mass (bioelectrical impedance spectroscopy and BMI *z* score) and is the first, to my knowledge, to investigate the impact of child genotype, despite limited power to detect interactions between peroxisome proliferator–activated receptor γ (PPARγ) genotype and treatment. Alternatively, Brei et al. (8) recruited women ($n = 208$) before 15 wk of gestation to an open-label, single-center RCT in Germany. The aim was to test the effects of reducing maternal n–6:n–3 LCPUFA ratio by using daily fish-oil capsules (1020 mg DHA + 180 mg EPA + 9 mg vitamin E) and an arachidonic acid (20:4n−6) balanced diet during pregnancy until 4 mo postpartum on child adiposity up to 5 y. This is one of the largest longitudinal data sets of combined methods (anthropometry, skinfold thicknesses, ultrasound, and MRI) to measure child body composition, including a subgroup of children ($n = 44$) who received the gold-standard abdominal MRI examination at 5 y. However, because the study was initially planned for a duration of only 12 mo, statistical power was lost during the extended follow-up period, which occurred annually from 1 to 5 y. Interestingly, mean maternal dietary DHA and EPA intakes reported by the control group in this study (~300 mg/d) were up to 3 times the intakes reported by women who were of childbearing age or pregnant (~90–200 mg/d) in Western countries (9–11). In contrast, no assessment of maternal dietary intake was included in the RCT by Muhlhausler et al.

The hypothesis that increasing the maternal intake of n–3 LCPUFAs during early adipose tissue development may prevent offspring adiposity is largely based on in vitro and animal models (5). Findings suggest that n–6 LCPUFA arachidonic acid promotes adipose tissue deposition, whereas n–3 LCPUFA EPA and DHA exert the opposite effect. Epidemiologic data since the early 20th century have reported a continuing shift toward an increased consumption of n–6 relative to n–3 LCPUFAs in the Western diet. This shift has further been observed in the diets of pregnant and lactating women over the past 2 decades and in the composition of breast milk. Although this hypothesis seems plausible as a possible strategy to help prevent childhood obesity, systematic reviews and meta-analyses of RCTs in human pregnancy continue to show no relation (2–4). The 3 systematic reviews and 1 meta-analysis that evaluated the effect of maternal n–3 LCPUFA supplementation during pregnancy and/or lactation on offspring adiposity all found considerable heterogeneity across included studies (2–4). Possible reasons include the timing of the intervention, type and dose of LCPUFA, sample size, and the choice of control regimen. Of interest here is that no RCT has examined the effect of reducing maternal n–6 PUFA

*To whom correspondence should be addressed. E-mail: michelle.blumfield@monash.edu.

[1] Abbreviations used: LCPUFA, long-chain PUFA; PPARγ, peroxisome proliferator–activated receptor γ; RCT, randomized controlled trial.

First published online May 18, 2016; doi: 10.3945/ajcn.116.136093.

intake on the development of offspring adipose tissue, which may, in fact, be more relevant given the role of n–6 PUFAs for fat cell development (6). Several large observational cohort studies investigated the relation between maternal (plasma LCPUFAs in mid- and late pregnancy) or fetal (LCPUFAs in umbilical cord blood) fatty acid status and child body composition (6). Although there is some evidence for a relation between LCPUFA intake and child adiposity, the lack of consistency between studies makes it difficult to draw any firm conclusions. Additional high-quality RCTs and follow-up analyses of ongoing studies are required to clarify the role of maternal fatty acid status in pregnancy.

This leads us to the question, What are the critical windows for adipose tissue development? Both Muhlhausler et al. (7) and Brei et al. (8) delivered their intervention in the second trimester. The intervention in the latter study was the earlier of the 2 RCTs, which began between 14 and 16 wk of gestation because the first appearance of adipocytes in the human fetus has been reported during this time period (8). However, evidence indicates that nutrient manipulation during embryonic and placental development (5–12 wk of gestation) can program offspring physiology. Therefore, it is possible that the critical window for adipose tissue development occurs earlier and was missed by the available literature. The importance of timing and duration of exposure to differing n–6:n–3 LCPUFA ratios warrants further investigation.

Both animal and human models suggest that adipose tissue at the abdominal and femoral sites is determined by different regulatory factors and variations in metabolic activity. It is likely the mechanism or mechanisms for early adipose tissue development may exhibit regional differences. We previously reported that maternal PUFA intake was positively associated with fetal midthigh lean area and inversely associated with fetal subcutaneous fat area (12). A relation between PUFA intake and abdominal adiposity was not observed (12). Findings support previous work that indicates that maternal PUFA intake during pregnancy may have an antiobesogenic effect and decrease fetal fat deposition (12). Although the use of abdominal MRI measurements at 5 y is a methodologic strength, it is not surprising that there was no significant difference in abdominal fat distribution between the intervention and control group observed by the researchers (8). Further high-quality research is required to confirm whether LCPUFA intake has an effect on adiposity in the gluteo-femoral regions.

Despite the benefits of causal relations and mechanistic insights, direct translation from animal models to human pregnancy is proving complex. At present, there does not appear to be any support for the use of maternal n–3 LCPUFA supplementation from the second trimester of pregnancy as a preventative strategy against childhood obesity. However, it remains unclear whether maternal n–3 LCPUFAs play a role if supplementation is commenced earlier in pregnancy. Future research is required to determine the critical window for the programming of offspring adipose tissue and to clarify whether regional differences in adiposity occur with n–3 LCPUFA supplementation. RCTs that recruit women during the preconception period with offspring follow-up and measurement of regional adipose tissue distribution are fundamental to confirm if maternal LCPUFA supplementation during preconception and/or pregnancy can program later obesity risk.

The author declared no conflicts of interest.

REFERENCES

1. Blumfield ML. Update on the role of maternal diet in pregnancy and the programming of infant body composition. Nutr Bull 2015;40:286–90.
2. Stratakis N, Gielen M, Chatzi L, Zeegers MP. Effect of maternal n-3 long-chain polyunsaturated fatty acid supplementation during pregnancy and/or lactation on adiposity in childhood: a systematic review and meta-analysis of randomized controlled trials. Eur J Clin Nutr 2014; 68:1277–87.
3. Rodríguez G, Iglesia I, Bel-Serrat S, Moreno LA. Effect of n-3 long chain polyunsaturated fatty acids during the perinatal period on later body composition. Br J Nutr 2012;107(Suppl 2):S117–28.
4. Muhlhausler BS, Gibson RA, Makrides M. Effect of long-chain polyunsaturated fatty acid supplementation during pregnancy or lactation on infant and child body composition: a systematic review. Am J Clin Nutr 2010;92:857–63.
5. Muhlhausler BS, Gibson RA, Makrides M. The effect of maternal omega-3 long-chain polyunsaturated fatty acid (n-3 LCPUFA) supplementation during pregnancy and/or lactation on body fat mass in the offspring: a systematic review of animal studies. Prostaglandins Leukot Essent Fatty Acids 2011;85:83–8.
6. Hauner H, Brunner S. Early fatty acid exposure and later obesity risk. Curr Opin Clin Nutr Metab Care 2015;18:113–7.
7. Muhlhausler BS, Yelland LN, McDermott R, Tapsell L, McPhee A, Gibson RA, Makrides M. DHA supplementation during pregnancy does not reduce BMI or body fat mass in children: follow-up of the DHA to Optimize Mother Infant Outcome randomized controlled trial. Am J Clin Nutr 2016;103:1489–96.
8. Brei C, Stecher L, Much D, Karla M-T, Amann-Gassner U, Shen J, Ganter C, Karampinos DC, Brunner S, Hauner H. Reduction of the n–6:n–3 long-chain PUFA ratio during pregnancy and lactation on offspring body composition: follow-up results from a randomized controlled trial up to 5 y of age. Am J Clin Nutr 2016;103:1472–81.
9. Meyer BJ. Australians are not meeting the recommended intakes for omega-3 long chain polyunsaturated fatty acids: results from an analysis from the 2011-2012 National Nutrition and Physical Activity Survey. Nutrients 2016;8(3):111–2.
10. Papanikolaou Y, Brooks J, Reider C, Fulgoni VL III. Adults are not meeting recommended levels for fish and omega-3 fatty acid intake: results of an analysis using observational data from NHANES 2003-2008. Nutr J 2014;13:31.
11. Givens ID, Gibbs RA. Current intakes of EPA and DHA in European populations and the potential of animal-derived foods to increase them. Proc Nutr Soc 2008;67:273–80.
12. Blumfield ML, Hure AJ, MacDonald-Wicks L, Smith R, Simpson SJ, Giles WB, Raubenheimer D, Collins CE. Dietary balance during pregnancy is associated with fetal adiposity and fat distribution. Am J Clin Nutr 2012;96:1032–41.