A Weighty Matter: Can PUFAs in Pregnancy Prevent Obesity?

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The prevalence of overweight and obesity has increased around the world and across all age-groups. In addition to reductions in physical activity and increases in the energy, sugar, and fat content of the diet, other contributors acting in early life are increasingly recognized, such as maternal obesity, gestational diabetes mellitus, antibiotic exposure, and maternal diet. Recently, in high-fat diet rodent models of maternal obesity, lowering the maternal ratio of n-6 to n-3 fatty acids using a novel genetic model or supplemental fish oil has been shown to prevent offspring obesity (1) and development of insulin resistance (1,2).

Reported in this issue of *Diabetes*, Rudolph et al. (3) used an elegant model to study the effects of a low maternal n-6/n-3 polyunsaturated fatty acid (PUFA) ratio on the propensity of the offspring to develop diet-induced obesity. They studied the offspring of the *fat-1* mouse, which expresses an enzyme not found in mammals that converts n-6 to n-3 PUFAs (4). Using this model instead of a nutritional intervention isolates the effects of the n-6/n-3 ratio from the potential confounding effects of diet. It also avoids the underrecognized problems associated with oxidation of PUFA-rich supplements or feed. Importantly, offspring exposed to a low maternal n-6/n-3 ratio were resistant to developing obesity and insulin resistance when challenged with a high-fat, high-sucrose "cafeteria" diet as adults. This may be explained, at least in part, by alterations in adipose tissue morphology and function, with greater cellularity, higher circulating adiponectin, altered gene expression, and increased methylation of PPARγ2. This study provides support for the idea that manipulation of maternal fatty acid levels during pregnancy might help to protect human offspring from developing obesity and metabolic disease in the modern obesogenic environment.

An important unanswered question is whether the reduced n-6/n-3 ratio acts primarily through changes in maternal metabolism or acts directly on the fetus. The effect could occur indirectly through increasing maternal insulin sensitivity and thereby reducing nutrient transfer to the fetus. Alternatively, the reduced n-6/n-3 ratio could act directly, reducing fetal production of prostacyclin, which is known to induce adipose tissue expansion.

Unfortunately, the elegant *fat-1* mouse model could not demonstrate whether the protective effect was a result of the low maternal n-6 PUFAs, the high n-3 PUFAs, or both. This distinction is important in the translation to human pregnancy, as it is easier to supplement with n-3 PUFAs than it is to restrict n-6 PUFAs. To clarify the specific roles of n-6 and n-3 PUFAs, an intricate dietary intervention study would be required.

Despite the positive findings in animal models, the human clinical trial evidence does not support a benefit of n-3 PUFA supplementation during pregnancy on reducing weight, BMI, or body fat of children (5–8). These trials were conducted predominantly in normal-weight women and supplemented n-3 PUFAs in the form of fish or algal oils using a wide range of doses (5–8). The largest trial followed up 1,531 children (7), and over 4,000 children have been studied in total (5–8). In one trial the intervention also included advice to restrict dietary n-6 PUFAs (6). However, it must be recognized that in the study of Rudolph et al. (3) in the *fat-1* mouse, there were no auxological differences in the offspring until after the high-fat, high-sucrose challenge in adulthood. With the exception of one study with substantial dropout (8), follow-up in human trials has only extended to school age (5–7), thus the children may not have become old enough, or had sufficient "nutritional challenge" from their Western diets, for the treatment groups to begin to diverge. This suggests that even if PUFA manipulation in human pregnancy is effective, it could be difficult to demonstrate and will require long follow-up. However, it is noteworthy that Rudolph et al. demonstrated differences in adiponectin concentration in the pups well before adulthood. Thus, if an intervention is effective, it may be possible to show differences in circulating metabolic markers or in functional indicators such as insulin sensitivity before differences in body composition emerge in adulthood.

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See accompanying article, p. 651.

COMMENTARY

In light of the disappointing results of previous trials that enrolled normal-weight mothers who have children with a low risk of obesity, a targeted approach focusing on obese pregnant women should be considered. The advantages of this approach are, first, that their children have a tendency to greater adiposity (9), so potential effects of PUFA manipulation on body composition may be easier to detect and with less requirement for the children to consume a poor diet. Second, the insulin-sensitizing effects of n-3 PUFAs may provide additional benefit in women who are obese. Obese pregnant women have exaggeration of the physiological insulin resistance of pregnancy, which leads to excessive delivery of glucose and lipid to the fetus (10). This fetal overnutrition is thought to lead to long-term adverse metabolic programming (10). n-3 PUFAs have now been demonstrated to be insulin sensitizing in humans (11,12), suggesting that if they improved maternal insulin sensitivity they might benefit the offspring indirectly through reducing nutrient transfer across the placenta.

Another important consideration is the point during gestation at which an intervention is started, as most previous human trials may have started too late. Studies in rodents typically begin the intervention at or prior to conception (the *fat-1* mouse is effectively a preconceptional intervention), although adipose tissue development occurs postnatally. In humans, adipose tissue development begins substantially earlier—between 14 and 16 weeks' gestation (13)—so PUFA manipulation may need to start prior to this time (14). Only two human studies started supplementation before the 16th week of pregnancy (6,8).

The quality of n-3 PUFA supplements is important but usually overlooked. n-3 PUFAs are labile and are frequently oxidized at the time of purchase (15–18). This oxidation alters their metabolic effects (19) and may increase their toxicity (20). Therefore, in trials of n-3 PUFAs during human pregnancy, the trial supplement should be assessed regularly for oxidation throughout the study period. Such quality assessment has not been performed in previous clinical studies.

Manipulating PUFAs in pregnancy could be a valuable tool in the prevention of obesity. However, the roles of lowering n-6 and/or raising n-3 PUFAs require clarification followed by translation to human pregnancy. Strategically, it may be more prudent to focus on obese rather than normal-weight pregnant women.

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