High-protein diets during pregnancy: healthful or harmful for offspring?1–3

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Maternal diet during pregnancy can induce developmental adaptations that permanently alter offspring physiology and metabolism (1). Fetal programming is an important risk factor for obesity- and adiposity-related noncommunicable diseases in adult life (1). The influence of maternal dietary protein during pregnancy on offspring phenotype and health is generating research interest (2, 3). Both low-protein (LP)4 and higher-protein (HP) diets during pregnancy have been associated with detrimental effects on offspring (3), suggesting a quadratic (U-shaped) relation and that macronutrient ratio may influence offspring health and disease. Research evaluating the optimal macronutrient ratio is required.

In this issue of the Journal, Maslova et al (4) present observations from a prospective Danish birth cohort of pregnant women recruited in 1988–1989 with offspring follow-up at age 19–21 y. This study is novel because it examines the long-term impact of maternal protein intake and protein quality during pregnancy on offspring anthropometric measures and biomarkers of adiposity and glucose metabolism. The study observed associations between higher maternal intakes of animal protein when substituted for carbohydrate [ie, higher animal protein-to-carbohydrate (P:C) ratio] with higher offspring BMI, primarily among females (4). This relation strengthened when models were adjusted for maternal age, education, parity, prepregnancy BMI, smoking, and sibling overweight. However, no associations were found between maternal protein intake and waist circumference or biomarkers of adiposity (4). Mean maternal protein intake [16% of energy (%E)] was comparable to that reported by pregnant women in developed countries (5). However, large variations in protein intake (9.5–40%E) during pregnancy have been recorded.

LP DIETS DURING PREGNANCY

Extensive animal research evaluating offspring health secondary to LP pregnancy diets has been reported for multiple organs and systems (3). Short-term effects in rodent models include impaired neonatal heart growth, with elevated blood pressure and impaired renal development found consistently from weaning to adult life (3). In pig models, offspring exposed to an LP diet (6.5% protein) grew more slowly and had greater fat mass than did those fed an HP diet (30% protein) (6). In rodents, longer-term effects include shortened life span (3), disturbed glucose homeostasis (3), disordered pancreatic proliferation and differentiation (7), hepatic steatosis (8), vascular dysfunction (3), increased susceptibility to oxidative injury (3), impaired immunity (3), altered feeding behavior (3), increased central fat deposition (3), hypertriglyceridemia and hypercholesterolemia (8), and reduced cerebral cortex capillary density in mature rodent offspring (3).

Human data by comparison are limited. The prospective Pune Maternal Nutrition Study reported that Indian infants (n = 631) born to predominantly vegetarian mothers with LP intakes (mean of 9.5%E) (1) were smaller in all body measurements but had similar subscapular skinfold-thickness measurements (9) compared with English infants (n = 338) born to UK mothers from Southampton (protein: 14.7%E) (10). This thin-fat phenotype predisposed children to insulin resistance (1). Additional research in the Southampton cohort found that higher maternal carbohydrate intakes in early pregnancy followed by lower dairy protein intakes in late pregnancy were associated with small placental size (10) and lower offspring ponderal index at birth (11). We recently reported in 156 mother-child dyads followed in pregnancy that maternal macronutrient profile was associated with fetal adiposity and fat distribution (2). Maternal protein intake was inversely associated with fetal abdominal subcutaneous fat at 36 wk of gestation, with fetal adiposity greatest when maternal dietary protein was low (<16%E) (2), whereas the proportion of fetal midlumbar subcutaneous fat area was greatest with intermediate maternal protein (18–21%E), high fat (40%E), and low carbohydrate (40%E) intakes (2). However, the UK Avon Longitudinal Study of Parents and Children (n = 5725) reported no associations between maternal pregnancy diet and child adiposity or lean mass as measured by dual-energy X-ray absorptiometry at ages 9 and 11 y (12).

Long-term findings from a prospective pregnancy cohort in Aberdeen, Scotland (n = 253), reported a relation between low maternal intake of animal protein (<50 g/d) with a reciprocal
higher carbohydrate intake (ie, low P:C ratio) and elevated blood pressure in middle-aged men. Each 100-g increase in carbohydrate was associated with a 3-mm Hg increase in systolic blood pressure ($P = 0.02$) (13). Interestingly, when maternal animal protein intake increased above 50 g/d, lower carbohydrate intake was also associated with higher blood pressure. Each 100-g decrease in carbohydrate was associated with an 11-mm Hg increase in systolic blood pressure ($P = 0.004$) (13). These findings support those found by Maslova et al (4) who reported an overall mean animal protein intake of 53 g/d, with mean intakes of 57 and 72 g/d in quartiles 3 and 4, respectively (4). Similar outcomes were reported in the Dutch Winter Hunger studies. Women who gave birth during the Dutch famine in 1944–1945 showed that offspring blood pressure in young adulthood was inversely associated with the P:C ratio of the average ration during the third trimester but not associated with any absolute measure of intake (14). This suggests that long-term health may be linked to the macronutrient ratio of maternal diet during late gestation. Thus, the relative importance of timing and duration of exposure to differing P:C ratios warrants further investigation.

**HP DIETS DURING PREGNANCY**

Less research has focused on HP diets during pregnancy. The Harlem Trial in 1976 found that consumption of HP (40 g protein) supplements during pregnancy was associated with higher preterm birth rates, lower birth weights, and a higher number of neonatal deaths (15, 16). From 1952 to 1976 in Motherwell, Scotland, pregnant women ($n = 626$) were advised to eat 1 pound (0.45 kg) of red meat/d and to avoid carbohydrate-rich foods to prevent preeclampsia (17). This HP diet provided 24.5%E from protein compared with 13.6%E in the usual Scottish diet (17). It was associated with reduced fetal growth (18), elevated offspring blood pressure at 27–30 y (17), and increased cortisol secretion in response to psychological stress in offspring at 36 y (19). This supports the Aberdeen study findings of elevated blood pressure in offspring whose mothers had consumed a high-animal-protein, low-carbohydrate diet in late pregnancy (13). Hence, HP supplementation/diets during pregnancy are not advised (16).

Studies that used manipulation to achieve HP (40%E) in gestational animal models reported defects in energy expenditure regulation (20) and higher offspring adiposity (3). Mice embryos from HP females had elevated concentrations of reactive oxygen species and ADP, indicating metabolic stress and possible uncoupling of oxidative phosphorylation (21), whereas embryos from LP females showed lower mitochondrial clustering around the nucleus, indicative of lower metabolic rate (21).

**DISCUSSION**

Even though it is accepted that a balanced maternal diet during pregnancy is important, research has focused on the consequences of gross nutrient deficiencies such as folate, iron, and protein-energy malnutrition, rather than macronutrient quality. Evidence is now emerging that small dietary changes may be associated with significant shifts in the fetal environment with associated long-term consequences (3). Internationally, there is a mismatch between dietary practices and macronutrient guidelines for diet in pregnancy (5), with different protein intake targets recommended (5). For example, the United States, Canada, the United Kingdom, and Europe recommend 10–35%E protein during pregnancy, whereas Australia/New Zealand and Japan recommend 15–25%E and &lt;20%E, respectively (5). Even within developed countries there is considerable variation in maternal protein intake, with younger mothers of lower socioeconomic status more likely to have lower protein intakes (3). In addition, the perceived risk of food-borne listeria infection leads some pregnant women to severely restrict important sources of high-quality protein, with adverse implications on diet quality, nutrient intakes, and pregnancy outcomes (22, 23). The challenge is to balance benefit and risk to achieve better maternal and offspring health outcomes.

Pregnant women need support to improve dietary intakes in developed as well as developing countries because of the changing food environment. We showed that a moderate protein intake (18–20%E) may support women to consume the largest variety of nutrients across all food groups (24). However, the findings from Maslova et al (4) suggest that if this moderate protein intake is made up largely of animal protein it could unfavorably increase offspring BMI in adult life (4). Antenatal nutritional advice with the aim of moderating energy and optimizing protein intake has been effective in reducing the risk of preterm birth and stillbirth and in increasing head circumference at birth (16).

Animal models provide a unique opportunity to manipulate the proportion of maternal protein intake during pregnancy. However, although causal relations and mechanistic insights can be gleaned, direct translation to human pregnancy is proving more complex. There may be an optimal protein-to-nonprotein ratio during pregnancy associated with offspring health. Prospective population-based pregnancy cohorts with offspring follow-up into adulthood are fundamental to confirm these relations.

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**REFERENCES**