Pregnancy: Impact of Maternal Nutrition on Intrauterine Fetal Growth

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This chapter of the YEARBOOK on NUTRITION AND GROWTH reviews important articles published between July 2016 and June 2017 concerning the impact of maternal nutrition during pregnancy on intrauterine fetal growth. We carefully selected human studies, mainly of randomized controlled or prospective design, along with several animal studies dealing with the effect of several nutrient supplementations on fetal growth and metabolic programming. This year, we focused on studies addressing the issue of fetal adiposity and maternal nutrition during pregnancy that may affect this outcome. Hopefully, this chapter will aid clinicians to update their knowledge on the effect of various intervention options and their effect on fetal growth and development.
Key articles reviewed for this chapter

Human Studies

Maternal dietary intake during pregnancy and offspring body composition: The Healthy Start Study
Crume TL, Brinton JT, Shapiro A, Kaar J, Glueck DH, Siega-Riz AM, Dabelea D
Am J Obstet Gynecol 2016;215:609.e1–e8

Maternal macronutrient intake during pregnancy is associated with neonatal abdominal adiposity: the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study
J Nutr 2016;146:1571–1579

Animal Studies

The early infant gut microbiome varies in association with a maternal high-fat diet
Chu DM, Antony KM, Ma J, Prince AL, Showalter L, Moller M, Aagaard KM
Genome Med 2016;8:77

Maternal blood lipid profile during pregnancy and associations with child adiposity: findings from the ROLO study
PLoS One 11:e0161206

Maternal diet quality in pregnancy and neonatal adiposity: the Healthy Start Study
Shapiro AL, Kaar JL, Crume TL, Starling AP, Siega-Riz AM, Ringham BM, Glueck DH, Norris JM, Barbour LA, Friedman JE, Dabelea D

Association of prenatal lipid-based nutritional supplementation with fetal growth in rural Gambia
Johnson W, Darboe MK, Sosseh F, Nshe P, Prentice AM, Moore SE
Matern Child Nutr 2017;13:e12367

The relationship between 25-hydroxyvitamin D concentration in early pregnancy and pregnancy outcomes in a large, prospective cohort
Boyle VT, Thorstensen EB, Mourath D, Jones MB, McCowan LM, Kenny LC, Baker PN. Baker on behalf of the SCOPE Consortium
Br J Nutr 2016;116:1409–1415

The effect of maternal nutrition level during the periconception period on fetal muscle development and plasma hormone concentrations in sheep
Sen U, Sirin E, Yildiz S, Aksoy Y, Ulutas Z, Kuran M
Animal 2016;10:1689–1696
**Maternal consumption of low isoflavone soy protein isolate alters hepatic gene expression and liver development in rat offspring**

Won SB, Han A, Kwon YH

*J Nutr Biochem* 2017;42:51–61

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**Human Studies**

**Maternal dietary intake during pregnancy and offspring body composition: the Healthy Start Study**

Crume TL, Brinton JT, Shapiro A, Kaar J, Glueck DH, Siega-Riz AM, Dabelea D

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**Background:** Animal models suggest that maternal dietary intake during pregnancy can affect the infant body composition. However, studies involving human population are lacking.

**Aims:** The current study aimed to explore the influence of maternal macronutrient intake and balance during pregnancy on neonatal body size and composition, including fat mass and fat-free mass.

**Methods:** This is an analysis of 1,040 mother-offspring pairs enrolled in a prospective observational cohort: the Healthy Start Study. Maternal diet during pregnancy was collected using dietary recalls (up to 8). Neonatal body composition was directly measured using air displacement plethysmography. Usual dietary intake during pregnancy was estimated using the National Cancer Institute measurement error model. The associations between maternal dietary intake and neonatal body composition were investigated by using multivariable partition (nonisocaloric) and nutrient density (isocaloric) linear regression models.

**Results:** The median macronutrient composition during pregnancy was 32.2% from fat, 15.0% from protein, and 47.8% from carbohydrates. In the partition multivariate regression model, no association was found between individual macronutrient intake values and neonatal birth weight or fat-free mass (FFM). However, an association was found between individual macronutrient and fat mass. About 418 kJ increases in total fat, saturated fat, unsaturated fat, and total carbohydrates were associated with 4.2 g (*p* = 0.03), 11.1 g (*p* = 0.003), 5.9 g (*p* = 0.04), and 2.9 g (*p* = 0.02) increase in neonatal fat mass, respectively. This increase was independent of maternal pre-pregnancy body mass index (BMI). In the nutrient density multivariate regression model, macronutrient balance was not associated with neonatal FFM, fat mass or birth weight after adjustment for pre-pregnancy BMI.
Conclusions: Increase in maternal intake of total fat, saturated fat, unsaturated fat, and total carbohydrates is associated with an increase in neonatal adiposity.

Comment

The association between maternal dietary intake during pregnancy and neonatal body composition is interesting and was mainly demonstrated in animal models. The relationship between maternal consumption of high-fat diet during pregnancy and the change in the offspring adiposity was previously demonstrated in rodent and other species. In contrast, human studies are less conclusive. Moreover, they are more prone to substantial methodological limitations as most studies of pregnant women have relied on food frequency questionnaires, which are prone to measurement error and are biased by patient self-reporting.

The clinical relevance of the findings of the current studies is several-fold. First, it is suggested that total energy intake sources contribute more than the calorie source as this study found that neonatal fat mass was influenced by various maternal macronutrients intake. Second, it is important to note that the magnitude of effect is small as a 418 kJ increase from saturated fatty acid is associated with only an 11.1 g or 4% increase in fat mass at birth. Yet, this increase is independent of maternal pre-pregnancy BMI, which is known to be correlated with neonatal adiposity. Third, this study provides evidence that the effect of maternal energy intake during pregnancy mainly affects the neonatal fat mass and had no detectable influence on FFM or even neonatal birth weight. The results of the study are important as they suggest potential nutritional interventions during pregnancy for the reduction of neonatal adiposity, without altering the overall neonatal body size or lean mass.

Maternal macronutrient intake during pregnancy is associated with neonatal abdominal adiposity: the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study

Chen LW1, Tint MT2, Fortier MV2, Aris IM7, Bernard JY7, Colega M7, Gluckman PD7,8, Saw SM4, Chong YS2,7, Yap P6,9, Godfrey KM10, Kramer MS2,11, van Dam RM3,4,12, Chong MF4,7,13, Lee YS1,7,14

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J Nutr 2016;146:1571–1579

Background: The body composition of infant was found to be associated with the risk for metabolic dysregulation later in life. However, not many have examined that the maternal macronutri-
ent intake may attenuate the neonatal body composition. Moreover, in most of the prior studies, a proxy measure of body composition was used, which may not reflect body fat distribution, particularly abdominal internal adiposity.

**Aims:** To investigate the influence of maternal macronutrient intake on neonatal abdominal adiposity measured in a multi-ethnic Asian mother-offspring cohort.

**Methods:** The current analysis includes 320 mother-offspring dyads with complete macronutrient intake and adiposity information. Maternal macronutrient intake was ascertained using a 24-h dietary recall at 26–28 weeks gestation. Neonatal abdominal adiposity was assessed using magnetic resonance imaging (MRI) in the second week of life. Associations were assessed by both substitution and addition models using multivariable linear regressions.

**Results:** The mean maternal age was 30 years. Maternal ethnicity diversity was as follows: 44% Chinese, 38% Malay, and 18% Indians. Mothers consumed 15.5 ± 4.3% (mean ± SD) of their energy intakes from protein, 32.4 ± 7.7% from fat, and 52.1 ± 9.0% from carbohydrate. A lower carbohydrate/fat higher protein diet during pregnancy was associated with lower neonatal abdominal internal adipose tissue (IAT; β [95% CI] –0.18 [–0.35 to –0.001] mL per 1% protein to carbohydrate substitution and –0.25 [–0.46 to –0.04] mL per 1% protein to fat substitution). These findings were more pronounced in males than in females (P-interactions <0.05). Higher maternal intake of animal protein (–0.26 [–0.47 to –0.05] mL for fat substitution), but not plant protein, was associated with lower offspring IAT. In contrast, maternal macronutrient intake was not consistently associated with infant anthropometric measurements, including abdominal circumference and subscapular skinfold thickness.

**Conclusions:** Increased maternal protein intake (as opposed to fat or carbohydrates) at 26–28 weeks of gestation was associated with lower abdominal internal adiposity in the offspring.

**Comment**

The rate of obesity in children and adulthood is rising and becoming a true epidemic in both developed and developing countries. Although overall adiposity is related to metabolic complication including hypertension and diabetes, many studies have reported that patients with increased visceral adipose tissue (intra-abdominal fat surrounding the internal organs) are at risk in particular. This may be due to the fact that adipocytes from visceral adipose tissue are more metabolically active and insulin-resistant compared with adipocytes from subcutaneous adipose tissue.

In this Asian multi-ethnic mother-offspring cohort study, higher maternal protein intake at the expense of carbohydrate or fat intake was associated with lower abdominal IAT in the newborns. The use of MRI for the assessment of visceral adiposity is a significant strength of this study as MRI is considered the gold standard method for this purpose. Another important point to consider in reviewing this study is that neonatal gender and maternal ethnicity modified the associations between maternal macronutrient intake and neonatal abdominal adiposity. The association of higher maternal protein intake and lower offspring IAT was stronger in boys.

Overall, the results of the study are important as optimizing maternal dietary balance during pregnancy might be a new approach to potentially improve the offspring body composition. Moreover, the traditional tools for the assessment of adiposity in the offspring are birth weight and anthropometric index. The lack of association between maternal macronutrient intake and various proxy measures of adiposity at birth indicated that accurate body fat distribution measurement early in life may provide more valuable insights on the risk for metabolic abnormalities.
The early infant gut microbiome varies in association with a maternal high-fat diet

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Genome Med 2016; 8:77

Background: Despite traditional presumption, emerging evidence suggests that the in utero environment is not sterile. Animal studies demonstrated transmission of commensal bacteria from mother to fetus during gestation, though it is unclear what modulates this process. In humans, maternal high-fat diet during pregnancy and lactation was previously found to persistently shape the juvenile gut microbiome.

Aims: This study aimed to interrogate whether a maternal high-fat diet similarly alters the neonatal and infant gut microbiome in early life in a population-based human longitudinal cohort.

Methods: A prospective cohort study of 163 women enrolling either in the early third trimester or intrapartum was used. Of them, 81 have consented to longitudinal sampling through the postpartum period. Samples were collected from multiple body sites of the neonates at delivery and by 6 weeks of age, including stool and meconium. Maternal nutrition over the past month prior to sample collection was assessed using a rapid dietary questionnaire to estimate intake of fat, added sugars, and fiber (National Health and Examination Survey). DNA was extracted from each infant meconium/stool sample (MoBio) and subjected to 16S rRNA gene sequencing and analysis.

Results: Maternal fat dietary intake ranged from 14.0 to 55.2%, with mean values of 33.1 ± 6.1%. Mothers whose diets significantly differed from the mean (±1 SD) were divided into two distinct groups: the control group (n = 13, μ = 24.4%) and a high-fat group (n = 13, μ = 43.1). Neonatal stool (meconium) analysis revealed differently clustered microbiome between the groups. Linear effect size (LEfSe) feature selection identified several taxa that discriminated the groups. Relative depletion of bacteroides was noticed in the group of neonates exposed to a maternal high-fat gestational diet, which persisted for 6 weeks of age.

Conclusions: Independent of maternal BMI, a maternal high-fat diet is associated with distinct changes in the neonatal gut microbiome at birth and even at 4–6 weeks of age. These findings highlight the importance of counseling pregnant mothers on macronutrient consumption during gestation and lactation.

Comment

The human microbiome encompasses a rich ecosystem of approximately 90 trillion microbes that aid in human metabolism and impact host physiology. It was previously found that microbiota is associated with the presence of obesity, inflammatory bowel disease, and autoimmune disease. In contrast to prior beliefs that the in-utero environment is sterile, recent data indicate that microbiota are present in the placenta and amniotic fluid of healthy, term pregnancies without any clinical evidence of infection. The findings of this study are important since not only the neonatal gut microbiome immediately after delivery revealed that it varied by virtue of maternal gestational diet, but also that this variation persisted for several weeks after birth. In the neonates of the maternal high-fat diet groups a relative depletion of bacteroides species in this early time period was found. This depletion may influence the infant’s fu-
ture risk of developing obesity. Yet, the literature to date is controversial regarding the association of bacteroides species and obesity, so whether such effect would be protective or contributory is unknown. It is important to note that maternal diet in the postpartum period was not explored in this study. Therefore, the effect of maternal diet and breast milk composition on the results regarding neonatal microbiome at 4–6 weeks of life cannot be assessed and may bias the results.

Although clear guidelines have been established for specific micronutrient and total caloric intake during gestation and lactation, the recommendations for macronutrients, including processed sugars, fats, and fibers are less. These findings, if proven in other large studies, may warrant consideration for refining dietary recommendations during pregnancy.

Maternal blood lipid profile during pregnancy and associations with child adiposity: findings from the ROLO study


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**Background:** It is well established that the in-utero environment affects fetal growth. Research concerning maternal hyperlipidemia has shown a relation with fetal growth mainly in women with hyperglycemia. However, this relationship in euglycemic women is scarce.

**Aims:** This study aimed to examine the relationship between maternal blood lipid profile and infant adiposity up to 2 years of age.

**Methods:** The ROLO (Randomized control trial of Low glycemic index diet vs. no dietary intervention in pregnancy to prevent recurrence of a large baby) study is a randomized trial that was conducted in Ireland in to assess whether low glycemic index in women with prior macrosomic infant may modulate the birth weight. In the current study, only data from 331 mother-child pairs were analyzed. Maternal dietary intakes were recorded and fasting blood lipids, leptin, and homeostatic model assessment index were measured in early and late pregnancy and cord blood. Infant anthropometric measurements and skinfold thicknesses were recorded at birth, 6 months and 2 years. Correlation and regression analyses were used to explore associations between maternal blood lipid status and infant adiposity.

**Results:** A significant increase in all maternal blood lipids during pregnancy was shown. Maternal dietary fat intake was positively associated with total cholesterol levels in early pregnancy. Late pregnancy triglycerides were positively associated with birth weight \((p = 0.03)\), while cord blood triglycerides were negatively associated with birth weight \((p = 0.01)\). Cord high-density lipoprotein cholesterol (HDL-C) was negatively associated with infant weight at 6 months \((p = 0.005)\). No other maternal blood lipids were associated with infant weight or adiposity up to 2 years of age.

**Conclusions:** An association was found between maternal and fetal triglycerides and birth weight. Cord HDL-C was found to be associated with weight at 6 months. Thus, maternal lipid concentrations may exert in-utero influences on infant body composition.

**Comment**

The rate of childhood obesity is increasing, with the World Health Organization estimating that over 41 million children aged under 5 years are obese. Obese children are
at increased risk for metabolic-related morbidity later in life, including type 2 diabetes, cardiovascular disease, and metabolic syndrome. Therefore, studies focusing on understanding variables associated with childhood obesity are of most importance, particularly those addressing the association between maternal diet during pregnancy and the child’s body composition. The current study is important, mainly because it is one of few prospective studies to have both maternal and fetal blood samples on multiple occasions during pregnancy, along with detailed infant anthropometry up to the age of 2 years. It demonstrated that dietary intakes of fat in early pregnancy were associated with total maternal cholesterol concentrations. In addition, it demonstrated that the concentrations of all blood lipids increased significantly as pregnancy progressed. Although these issues were previously studied, the current study adds to the current knowledge of associations between maternal blood lipid concentrations during pregnancy and outcomes for the baby. In addition, the finding regarding the association of higher HDL-C concentrations in cord blood and lower infant weight at 6 months was not previously reported. As maternal diet during pregnancy is modifiable, this represents a way to potentially reduce childhood obesity levels. Yet, it is important to remember that the cohort of the ROLO study was a high-risk group for macrosomia and further research should be conducted before official recommendation can be made in the general obstetric population.

Maternal diet quality in pregnancy and neonatal adiposity: the Healthy Start Study

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**Background:** Maternal diet in pregnancy can influence fetal growth and development.

**Aims:** To test the hypothesis concerning an association between poor maternal diet quality during pregnancy and increase in neonatal adiposity (percent fat mass [%FM]) at birth.

**Methods:** An observational cohort of 1,079 mother-offspring pairs was used. For each woman, Healthy Eating Index-2010 (HEI-2010) scores were calculated according to maternal diet, which was assessed via repeated Automated Self-Administered 24-h dietary recalls. The scores in the HEI-2010 was dichotomized into scores of ≤57 and >57. Lower scores represented poorer diet quality. Within 72 h after delivery, neonatal %FM was assessed using air displacement plethysmography. The relationship between maternal diet quality and neonatal %FM, FM, and fat-free mass were explored while adjusting for potential confounders including pre-pregnancy BMI, physical activity, maternal age, smoking status, energy intake, hypertensive disorders during pregnancy, infant sex, and gestational age at delivery.
Results: The total HEI-2010 score ranged between 18.2 and 89.5 (mean: 54.2, SD 13.6). An HEI-2010 score of ≤57 was significantly associated with higher neonatal %FM (β = 0.58, 95% CI 0.07–1.1, \( p < 0.05 \)) and FM (β = 20.74; 95% CI 1.49–40.0; \( p < 0.05 \)) but no difference in fat-free mass was observed.

Conclusions: Neonatal adiposity is increased in cases of poor maternal diet quality during pregnancy independent of maternal pre-pregnancy BMI and total caloric intake.

Comment Maternal obesity was found to be associated with increased birth weight and neonatal adiposity in large prospective cohort studies. In turn, these offsprings are at greater risk for childhood obesity and future metabolic dysregulation. Unfortunately, it is challenging to implement interventions that can successfully help women to maintain proper weight before becoming pregnant, partly because a significant portion of pregnancies are unplanned. Therefore, research should be shifted from reducing maternal weight before and during pregnancy to other interventions that may also affect fetal overgrowth and offspring adiposity, including the improvement of maternal diet and nutrition. The present analysis aimed to fill this information gap using the Healthy Start cohort, a pre-birth, multi-ethnic cohort of 1,410 mother-offspring pairs. The importance of this study lies in the fact that while maternal nutrition during pregnancy has been previously studied in relation to birth outcomes, this study focuses on the effect of maternal diet quality during pregnancy on neonatal body composition, which was scarcely studied before. The researchers demonstrated that lower maternal diet quality has a significant impact on neonatal adiposity, irrespective of maternal pre-pregnancy BMI. Of note, neonates of women with lower diet quality had a mean increase of 24.9 g of fat mass, compared with those whose mothers had a higher diet quality. In comparison, the mean effect of maternal obesity on neonatal fat mass was 47.5 g (obese vs. normal weight mothers). This finding highlights the magnitude of diet quality among other effectors of fetal and neonatal adiposity and the potential importance of dietary interventions during pregnancy.

Association of prenatal lipid–based nutritional supplementation with fetal growth in rural Gambia

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Background: Prenatal supplementation with protein-energy (PE) and/or multiple-micronutrients (MMNs) may improve fetal growth, however, inconsistent evidence exists regarding lipid-based nutritional supplements (LNS) and its relation to fetal growth.

Aims: The aim of the study was to explore the association between LNS during pregnancy and fetal growth, and explore how efficacy varies depending on the nutritional status.

Methods: A post-hoc analysis of non-primary outcomes in a trial in Gambia was conducted. Pregnant women (\( n = 620 \)) were individually randomized, into 4 arms: (a) iron and folic acid tablet (usual care, referent group), (b) MMNs tablet, (c) PE + LNS, and (d) PE + LNS + MMNs tablet. Analysis of variance examined unadjusted differences in fetal biometry z-scores at 20 and 30 weeks and neonatal anthropometry z-scores, while regression tested for modification of intervention-
outcome associations by season and maternal characteristics including maternal height, BMI, and weight gain during pregnancy.

**Results:** Z-scores at birth were not greater in the intervention arms than the FeFol arm (e.g., birth weight z-scores: FeFol –0.71, MMN –0.63, PE –0.64, PE + MMN –0.62; group-wise \( p = 0.796 \)). In regression analyses, intervention associations with birthweight and head circumference were modified by maternal weight gain between booking and 30 weeks gestation (e.g., PE + MMN associations with birth weight were +0.462 z-scores (95% CI 0.097–0.826) in the highest quartile of weight gain but –0.099 z-scores (–0.459 to 0.260) in the lowest).

**Conclusion:** No strong evidence was found regarding the use of prenatal LNS and improvement in fetal growth in the study sample. However, some improvement was noticed in the subgroup of women who had the highest weight gain.

**Comments**

It is estimated that almost half of pediatric mortality is related to undernutrition in the developing countries, with fetal growth restriction alone accounting for 12% of deaths. It was hypothesized that a balanced prenatal protein-energy (PE) and MMN supplementation could potentially reduce fetal growth restriction and that the impact may be best observed in women who are more nutritionally vulnerable, like in rural Gambia. Although the results of the current study failed to demonstrate any association between prenatal LNS intervention and better fetal growth in the whole sample, it was found to have an additional value in the subgroup of women who demonstrated the greatest gestational weight gain. It implies that prenatal LNS intervention cannot be a substitution for a balanced diet and for proper nutrition during pregnancy and that we need to take all efforts to make sure that women will have proper diet and will be well-nourished especially during the pregnancy period. Only after we accomplish this objective, will we add interventions, like LNS, to improve fetal growth.

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**The relationship between 25-hydroxyvitamin D concentration in early pregnancy and pregnancy outcomes in a large, prospective cohort**

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**Background:** Low plasma vitamin D levels have been associated with an increased rate of complications in pregnancy. Controversy remains as findings have been inconsistent between disparate populations.

**Aims:** The aim of the current study was to explore the association between vitamin D status and the risk for adverse pregnancy outcomes.

**Methods:** A large, prospective cohort study was conducted. Maternal 25-Hydroxyvitamin D concentration in serum samples collected at 15 weeks of gestation from 1,710 New Zealand women was
analyzed. The associations between vitamin D status and pre-eclampsia, preterm birth, small for gestational age (SGA), and gestational diabetes were investigated.

**Results:** The mean vitamin D level was 72.9 nmol/L. Overall, only 23% had 25-hydroxyvitamin D concentrations <50 nmol/L, and 5% of women had concentrations <25 nmol/L. Those with vitamin D concentrations <75 nmol/L at 15 weeks of gestation were at increased risk for gestational diabetes mellitus than those with concentrations >75 nmol/L (OR 2.3; 95% CI 1.1–5.1). This effect was not significant when adjustments were made for BMI and ethnicity. No increased risk was found regarding the risk for preeclampsia, preterm birth or SGA infants.

**Conclusion:** In this vitamin D-replete pregnancy cohort, 25-hydroxyvitamin D concentration at 15 weeks of gestation did not predict pregnancy outcomes including preeclampsia, SGA, spontaneous preterm birth, and GDM when adjustments were made for confounders.

**Comments**

There is a controversy in the literature regarding the vitamin D supplementation during pregnancy. Some studies, including a recently published meta-analysis [1] found no difference in the rate of SGA or low birth weight with vitamin D supplementation in pregnancy. However, another systemic review on vitamin D supplementation in pregnancy found a reduced incidence of preeclampsia, preterm birth, and low birth weight (<2,500 g) [2]. In this prospective study, maternal vitamin D levels were not found to be associated with pregnancy-related complications. The execution of studies exploring the association between vitamin D levels and birth weight among other complication is not easy. There are many etiologies for reduced birth weight and controlling for potential confounders is not an easy task. Moreover, it is important to notice that vitamin D status in the population itself (vitamin D replete vs. deplete population) may also affect the results in studies addressing the added value of vitamin D supplementation. In addition, vitamin D may be a surrogate marker for other causative factors that vary between populations, particularly those with seasonal variation. Finally, the ethnic group studied may also affect the results since genetic polymorphisms of the vitamin D nuclear receptor and vitamin D binding protein exists. The most important take home message from the current study is to understand its setting and methods and to be cautious in translating the results to other populations.
The effect of maternal nutrition level during the periconception period on fetal muscle development and plasma hormone concentrations in sheep

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Animal 2016; 10:1689–1696

Background: Maternal malnutrition during gestation may alter fetal growth, and newborn’s growth and development.

Aims: To examine the association between maternal nutrition during the periconception period and the muscle development of fetus and maternal-fetal plasma hormone concentrations in sheep.

Methods: Estrus was synchronized in 55 Karayaka ewes and were either fed ad libitum (well-fed [WF], \(n = 23\)) or 0.5× maintenance (under-fed [UF], \(n = 32\)) 6 days before and 7 days after mating. Those who did not become pregnant and ewes carrying twins and female fetuses were excluded from the study. Singleton male fetuses from WF \((n = 8)\) and UF \((n = 5)\) ewes were collected on day 90 of gestation and placental characteristics, fetal birth weight and dimensions, fetal organs and muscles weights were recorded. Maternal and fetal blood samples were collected on day 7 after mating and on day 90 of pregnancy, respectively, and plasma hormone concentrations were analyzed.

Results: Maternal nutrition during the periconception period had no statistically significant effect on placental characteristics, birth weight and dimensions, organs and muscles weights of the fetuses. In addition, maternal intake did not affect fiber numbers and the muscle cross-sectional area of the fetal longissimus dorsi (LD), semitendinosus (ST) muscles, but the cross-sectional area of the secondary fibers in the fetal LD and ST muscles from the UF ewes were higher than those from the WF ewes \((p < 0.05)\). Moreover, a lower ratio of secondary to primary fibers in the ST muscle was tended in fetuses from the UF ewes. Regarding plasma concentration of hormones, no significant changes in fetal plasma insulin and maternal and fetal plasma IGF-I, cortisol, progesterone, free T3 and T4 concentrations were noted between the groups. However, maternal cortisol concentrations were lower while insulin concentrations were higher in the WF ewes than those in the UF ewes.

Conclusions: In lambs, reduced maternal feed intake during the periconception period may alter muscle fiber diameter without affecting fiber types, fetal weights and organ developments and plasma hormone concentrations in fetus.

Comment Maternal undernutrition during gestation not only affects nutrient and hormone concentrations in blood, but may also change the intrauterine micro-environment. This in turn may affect placental-fetal development, and therefore, influence subsequent development of the offspring. In addition, maternal endocrine status was previously shown to be affected by maternal nutrition level during the periconception period. The findings of the current study suggest that low nutrient intake during the periconception period affect the cross-sectional area of secondary fibers (in LD and ST mus-
cles) and changes the ratio of secondary to primary fibers (in ST muscle). Of note, despite these effects, no changes were observed regarding fetal weights, placental characteristics, fetal organ developments, and fetal plasma hormone concentrations. These findings are important since these microscopic changes may go unnoticed when only clinical parameters such as birth weight are studied. These results teach us to explore microscopic effects that may have long-term outcomes and not only focus on the obvious outcome measures. Future studies may explain the underlying mechanisms involved in early embryonic development and programming of the muscle cell lineage.

Maternal consumption of low isoflavone soy protein isolate alters hepatic gene expression and liver development in rat offspring

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Background: Fetal growth and development are known to be affected by the In utero environment. More specifically, in offspring exposed to soy protein isolate (SPI) or genistein, a distinct fetal programming of carcinogenesis was reported.

Aims: The aim of the current study was to investigate whether hepatic gene expression and liver development of rat offspring is altered by maternal consumption of low-isoflavone SPI or genistein.

Methods: A 3-arms interventional study was conducted. Female Sprague-Dawley rats were fed a casein diet, a low-isoflavone SPI diet or a casein diet supplemented with genistein (250 mg/kg diet) for two weeks before mating and throughout pregnancy and lactation. Male offsprings were studied on postnatal day 21 (CAS, SPI and GEN groups).

Results: Among 965 differentially expressed hepatic genes related to maternal diet (Pb.05), a significantly different expression of 590 was found between the CAS and SPI groups. When comparing the CAS and GEN groups, the expression of 88 genes was significantly different between the groups. This difference mainly involved genes related to drug metabolism that were significantly affected by maternal diet.

Conclusions: Maternal consumption of a low-isoflavone SPI diet alters the hepatic gene expression profile and liver development in offspring possibly by epigenetic processes.

Comments

Data from both human and animal studies indicate that maternal nutrition and other environmental factors can alter the in utero development, which may further result in changes in the offspring susceptibility of chronic disease later in life. These modifications have been proposed to occur by altering epigenetic state of the fetal genome, such as DNA methylation and post-translational histone modification, caused by maternal nutrition.

The current study was aimed to determine whether maternal consumption of a low-isoflavone SPI diet and a casein diet supplemented with genistein could alter the hepatic gene expression and liver development in rat offspring. Despite the fact that previous studies have demonstrated the effect of maternal diet on the development of metabolic disease in the offspring, the use of gene expression profiling in a specific organ of young offspring was not extensively studied before.
The results of the current study suggest that the hepatic gene expression may be altered by amino acid composition or other bioactive components of SPI rather than soy isoflavone per se. An increased cell proliferation, reduced apoptosis, and activation of the mTOR pathway were shown in the SPI group. This may have contributed to a higher relative liver weight compared to other groups. In addition, the researchers observed higher serum homocysteine levels and lower global and CpG site-specific DNA methylation of Gadd45b, a gene involved in cell proliferation and apoptosis, in SPI group compared to CAS group. These observations are not only interesting, but also important. We believe that in the era of extensive gene research, more studies assessing the influence of maternal diet on neonatal gene expression (in different end organs) should be performed to support studies addressing only clinical parameters.

**Overall commentary**
Adiposity and its related comorbidities has become prevalent worldwide, with the World Health Organization estimating that over 40 million children aged under 5 years are obese. There is no single method to define neonatal adiposity. Therefore, in the current chapter, novel studies addressing this issue in various perspectives were presented and discussed. Although maintaining a balanced maternal diet may improve offspring outcome, the impact of nutrition on fetal/offspring growth and development is also attenuated by genetic, demographic, behavioral, and other factors. Thus, maternal nutrition, like any other intervention, should be personalized to achieve its maximal benefit.

**Disclosure Statement**
The authors report no conflict of interest.

**References**