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Furthering the understanding of maternal obesity in NAFLD

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Keywords

Children; gestational weight gain; pregnancy; nonalcoholic fatty liver disease; high fat diet; sugar sweetened beverages

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in children today and the prevalence has more than doubled over the past decade.(1) From an epidemiologic standpoint, the rapid rise in NAFLD outpaces the increase in obesity.(1) This is concerning given the current and future burden of pediatric NAFLD to individuals and the healthcare system. Our understanding of pediatric NAFLD and its etiology continues to evolve. One major contributor appears to be diets high in sugar and fat leading to the development of obesity, increased adipose insulin resistance and subsequent hepatic steatosis. The search for other, non-dietary contributors to pediatric NAFLD has prompted researchers to pursue genetic, epigenetic and other causes. In the paper by Mouralidarane and colleagues, they explore the complex interplay between maternal diet, gestational environment, and the developing innate immune system. It seems that the development NAFLD begins even before children have a chance to eat on their own.

Maternal weight gain during pregnancy is known to have persistent effects on offspring with relation to post-natal intake, food choices and development of obesity; although this has been best shown in animal models. Mice fed a high fat diet during pregnancy (resulting in excess maternal weight gain) have offspring that gain more weight(2) and prefer highly palatable foods.(3) This was translated to humans in a large study demonstrating that maternal fat consumption (and not paternal) was associated with fat preference by the child, and that this led to a greater incidence of obesity in offspring.(4) Offspring born to mice fed a high fat diet during gestation also have increased insulin resistance, hepatic steatosis and liver injury.(2, 5) These changes may be programmed by defects in lipid and carbohydrate metabolism causing inability to adapt to postnatal diet. For example, sterol regulatory element-binding protein-1c (SREBP-1c), a transcription factor that stimulates key lipogenic genes is increased in the offspring of maternal high fat diet.(2) Glut-2 has been shown to be decreased suggesting impaired metabolism of carbohydrates. All of this was associated with increased TNF-α, decreased hepatic mitochondrial electron transport chain enzyme complex activity and liver inflammation in the offspring simply from high fat diet during gestation.(2, 5, 6)

The roles for maternal and child dietary composition, and the potential for novel understanding of the response of non-parenchymal cells and innate immunity in liver is explored by Mouralidarane et al(7). In their study, offspring of obese mice fed a high fat/ high sugar diet during gestation appeared to be sensitized to a post-natal obesogenic diet because they developed more severe weight gain, hypertriglyceridemia, hepatic inflammation and fibrosis compared to those exposed either during pregnancy alone or post-

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natally alone. Interestingly, the dual effect of prenatal and postnatal obesogenic diets appeared to be more than additive in its effect on hepatic fat. Maternal obesity alone did not cause significant weight gain or hepatic fat in the offspring.

One issue with the experimental design used by Mouralidarane et al. is the inability to assess if the effects are from the gestational weight gain or from the specific macronutrient change. Previous studies have shown fructose and fat have effects on offspring without gestational weight gain.(2, 8) Fructose in the water of pregnant Wistar rats induced SREBP-1c mRNA and protein expression and fatty acid synthase mRNA expression in the fetal livers without significant weight gain in the dams.(8) While it is difficult to separate effects of weight gain from high fat and/or high fructose diets during gestation, this is a potential area of future research that has important implications for public health. Another important distinction is if increased body weight, fat mass and hepatic fat in the offspring of obese mothers was from increased consumption compared to those without obese mothers. Given the previous work demonstrating increased fat preference by offspring it would be interesting to know if the feeding behavior was altered by the maternal obesity or if the effects were transmitted through decreased tolerance of the post natal obesogenic diet.

Mouralindarane et al also examined the role of innate immune system dysfunction. They documented increased kupffer cells numbers, impaired phagocytic function of the kupffer cells and increased ROS production in the mice with pre and post-natal exposure to the obesogenic diet. Decreased function of kupffer cells is an important area of interest in the mechanism of NAFLD. Impaired clearance of lipopolysaccharide (LPS) by kupffer cells could result in accelerated liver injury (9), as seen in the pre and post natal exposed offspring. The innate immune system has been previously demonstrated to be altered by diet. High fat feeding in mice resulting in increased body weight and hepatic steatosis causes selective NKT cell depletion in the liver and is associated with increase production of pro-inflammatory cytokines such as TNF-α and IFN-γ.(6) This is consistent with the findings of Mouralindarane et al which again demonstrated a decrease in NKT cells in the liver in response to a postnatal high fat/high sugar diet. They add to the picture by demonstrating further depletion in the combined group compared with post natal exposure alone.

In conclusion, this article and others demonstrate a powerful influence of maternal obesity and a gestational obesogenic diet to sensitize the offspring to induction of NAFLD. This multiplicative effect is important because it could help explain the rapid rise in pediatric NAFLD. Further, the combination of pre and post natal exposure to the diet resulted in a NASH like picture with increased pro-fibrogenic markers, increased fibrosis in the liver and increased inflammation associated with alterations in innate immunity. This has particular relevance to the consideration of why some children have severe features of NASH at relatively young ages. The findings lend support for carefully designed human studies, particularly for populations known to be at high risk for NAFLD.

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Abbreviations

NAFLD	nonalcoholic fatty liver disease
SREBP-1c	sterol regulatory element-binding protein-1c
TNFα	tumor necrosis factor α

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