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Perinatal Programming of Adolescent Nonalcoholic Fatty Liver Disease: A Case for Gender Inequality?

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Nonalcoholic fatty liver disease (NAFLD) is a prevalent condition strongly related to obesity with a spectrum ranging from steatosis to steatohepatitis and a risk of progression to cirrhosis and major complications. NAFLD in children and adolescents often has a more aggressive course. It is therefore particularly alarming that up to 20% of the general pediatric population and 80% of obese children in the Western world are now diagnosed with NAFLD. There are considerable efforts to explore and eliminate the drivers of pediatric obesity and associated disorders. Evidence shows that perinatal exposure to environmental challenges may dramatically impact health trajectories in later life. The concept of developmental programming postulates that facing adversities during a critical window of development may lead to permanent and even inheritable changes in physiological regulation, primarily through epigenetic mechanisms such as DNA methylation, histone modification, and noncoding RNAs.⁽¹⁾

Early life factors such as prepregnancy obesity, maternal obesity, and abnormal gestational weight gain have been associated with increased rates of obesity in the offspring.⁽²⁾ However, little is known about how adverse metabolic environments in perinatal life may affect postnatal development of NAFLD. Moreover, it remains unclear whether these changes persist later in life. In this issue of Hepatology, Ayonrinde et al. expand upon earlier findings regarding developmental programming for NAFLD.⁽³⁾ The authors analyzed the Western Australian Pregnancy (Raine) Cohort Study for the perinatal history of 1170 adolescent offspring diagnosed with NAFLD by liver ultrasound at age 17. One of the most extensive longitudinal surveys of pregnancy and childhood, the Raine study enrolled 2979 women by week 18 of gestation from the antenatal clinic of King Edward Memorial Hospital in Perth, and in the past 27 years a total of 2868 children from this cohort have been followed up at birth and every few years thereafter.

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Multiple regression analysis by Ayonrinde et al. established a striking sexual dimorphism with regard to perinatal predictors of adolescent NAFLD.⁽³⁾ Thus, after adjusting for adolescent obesity, maternal prepregnancy obesity and gestational weight gain >6 kg by week 18 independently predicted NAFLD in adolescent girls, whereas lower socioeconomic status at birth was the only independent predictor of NAFLD in adolescent boys. Moreover, maternal obesity was associated with higher serum leptin, glucose, and insulin levels and higher homeostatic model assessment for insulin resistance (HOMA-IR) scores in adolescent girls, but higher serum leptin only in boys. Paternal prepregnancy obesity predicted NAFLD and increased serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels only in adolescent boys, indicating an assortative (i.e., father-to-son) effect.⁽³⁾ In an earlier analysis of the Framingham Heart Study, paternal but not maternal early onset obesity was linked to higher serum ALT levels in the offspring, although in that study no association with serum AST levels and no gender differences were reported, and the average age of the offspring cohort was 42 years (4), suggesting that findings in these two studies may reflect differences between adolescent and adult NAFLD.

Ayonrinde et al. speculate that the association of lower socioeconomic status with increased risk of NAFLD in adolescent boys may be related to shorter breastfeeding, because lower socioeconomic status was only associated with <6 months of exclusive breastfeeding in boys, but not in girls.⁽³⁾ Indeed, within the Raine cohort, breastfeeding has been shown to protect against the development of NAFLD in adolescents,⁽⁵⁾ which may relate to regulation of self-feeding, improved insulin sensitivity, and regional fat mobilization. In addition to the benefits in offspring, data presented at the 2016 American Association for the Study of Liver Diseases meeting showed that longer duration of breastfeeding (>6 months versus < 1 month) was associated with approximately half the odds of prevalent NAFLD in mothers in midlife.⁽⁶⁾ These findings mirror other long-term benefits of breastfeeding in mothers, such as lower risk of cardiovascular disease and diabetes. Although the reason for faster weaning of boys in the Raine cohort remains unclear, the findings corroborate the relationship of childhood socioeconomic disadvantage with adulthood obesity. Given the expansive benefits on maternal and child metabolic health, encouragement of nursing may be an additional focus in our global effort to reduce the disease burden of obesity and its associated complications, including NAFLD.

The current study also raises questions about the sex hormone environment of the growing fetus, and how this may differentially affect metabolic risk in male and female offspring. In a prior Raine study, 16% of adolescent girls were diagnosed with polycystic ovary syndrome (PCOS); a common endocrine disorder characterized by insulin resistance, obesity, and elevated androgens.⁽⁷⁾ Adolescent boys and PCOS girls with NAFLD had greater body mass index, visceral adiposity, and HOMA-IR than girls with NAFLD without PCOS. In that study, androgens were not independently associated with NAFLD risk, though recent data demonstrate such association in women, which is believed to be largely mediated by visceral adiposity.⁽⁸⁾ In animal models, prenatal androgen exposure results in alterations in adipocyte lipolysis, hepatic lipid metabolism, and glucose intolerance, with sustained metabolic derangements into puberty and adulthood.⁽⁹⁾ In adults there is a sexually dimorphic effect of androgens on metabolic comorbidities with increasing testosterone levels predisposing to these conditions in women, while testosterone appears to protect against diabetes, visceral

adiposity, and NAFLD in men.⁽¹⁰⁾ Whether there are similar sexually dimorphic effects of prenatal androgen exposure on NAFLD risk in male compared with female offspring warrants further exploration.

The study by Ayonrinde et al. enhances our understanding of how perinatal factors may shape the development of adolescent NAFLD.⁽³⁾ However, there are several caveats to consider before generalizing these findings. First, the cohort represents the population of Western Australia with 90% of Caucasian ethnicity. Ethnicity has a significant influence on the distribution of genetic polymorphism (and plausibly epigenetic signatures) associated with NAFLD, making the results potentially difficult to extrapolate to more diverse populations. Second, NAFLD was diagnosed with ultrasound, which limits association of specific disease features with perinatal factors. Third, there is limited information about the environments that affected NAFLD development during the 17 years of the cohort. The authors applied adult guidelines to exclude male and female subjects who reported weekly alcohol consumption of >210 g and >140 g, respectively. However, this is a generous threshold for teenage drinking, and the contribution of alcohol to steatosis remains unclear. Finally, epigenetic changes are not reset to zero for each reproductive cycle and metabolic vulnerability may accumulate through subsequent generations. This analysis pertains to pregnancies between 1989 and 1992 that predated the obesity epidemic. As more obese adolescents enter reproductive years, this could be the tip of the iceberg with NAFLD phenotypes accelerating in future generations.

Lifestyle modification remains the cornerstone of NAFLD management, with weight loss, dietary interventions, and exercise interventions being most effective at decreasing hepatic fat. Unfortunately, compliance with lifestyle interventions remains challenging, and many patients have difficulty initiating or maintaining these regimens. However, knowing the deleterious effects of individual behaviors on the health of one's offspring can be a powerful motivator, and often leads to cessation of other addictive behaviors, such as alcohol and tobacco use. Therefore, educating patients about the risk that their own obesity confers to their children should be incorporated into standard counseling. Herein lies the individual and societal responsibility to breaking the intergenerational transfer of obesity and associated disorders such as NAFLD. Because at the end of the day, it's all about family.

Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
HOMA-IR	homeostatic model assessment for insulin resistance
NAFLD	nonalcoholic fatty liver disease
PCOS	polycystic ovary syndrome

References

1. Barker DJ. The origins of the developmental origins theory. *J Intern Med.* 2007; 261:412–417. [PubMed: 17444880]
2. Haire-Joshu D, Tabak R. Preventing obesity across generations: evidence for early life intervention. *Annu Rev Public Health.* 2016; 37:253–271. [PubMed: 26989828]
3. Ayonrinde OT, Adams LA, Mori TA, Beilin LJ, de Klerk N, Pennell CE, et al. Sex differences between parental pregnancy characteristics and nonalcoholic fatty liver disease in adolescents. *Hepatology.* 2018; 67:108–122. [PubMed: 28665032]
4. Loomba R, Hwang SJ, O'Donnell CJ, Ellison RC, Vasan RS, D'Agostino RB Sr, et al. Parental obesity and offspring serum alanine and aspartate aminotransferase levels: the Framingham heart study. *Gastroenterology.* 2008; 134:953–959. [PubMed: 18395076]
5. Ayonrinde OT, Oddy WH, Adams LA, Mori TA, Beilin LJ, de Klerk N, et al. Infant nutrition and maternal obesity influence the risk of non-alcoholic fatty liver disease in adolescents. *J Hepatol.* 2017; doi: 10.1016/j.jhep.2017.03.029
6. Ajmera V, Terrault N, VanWagner L, Sarkar M, Lewis CE, Carr JJ, et al. Longer lactation duration is associated with decreased non-alcoholic fatty liver disease in the CARDIA cohort study. *Hepatology.* 2016; 63(Suppl 1):111.
7. Ayonrinde OT, Adams LA, Doherty DA, Mori TA, Beilin LJ, Oddy WH, et al. Adverse metabolic phenotype of adolescent girls with non-alcoholic fatty liver disease plus polycystic ovary syndrome compared with other girls and boys. *J Gastroenterol Hepatol.* 2016; 31:980–987. [PubMed: 26589977]
8. Sarkar M, Wellons M, Cedars MI, VanWagner L, Gunderson EP, Ajmera V, Torchen L, et al. Testosterone levels in premenopausal women are associated with nonalcoholic fatty liver disease in midlife. *Am J Gastroenterol.* 2017; 112:755–762. [PubMed: 28291240]
9. Abruzzese GA, Heber MF, Ferreira SR, Velez LM, Reynoso R, Pignataro OP, et al. Prenatal hyperandrogenism induces alterations that affect liver lipid metabolism. *J Endocrinol.* 2016; 230:67–79. [PubMed: 27179108]
10. Schiffer L, Kempegowda P, Arlt W, O'Reilly MW. Mechanisms in endocrinology: the sexually dimorphic role of androgens in human metabolic disease. *Eur J Endocrinol.* 2017; 177:R125–R143. [PubMed: 28566439]

FIG. 1.

Perinatal programming and sexual dimorphism in the development of adolescent NAFLD. Major periods of early life and potential mechanisms of metabolic vulnerabilities leading to NAFLD are illustrated schematically. The offspring genome assembled at conception includes genetic variance (e.g., single nucleotide polymorphism) and nongenetic effects of parental life experiences via gamete imprinting that may drive future susceptibility to disease. Gene expression and function is further modified by environmental effects during gestation and in postnatal life with a heritable impact (epigenetic modifications) or with changes limited to the individual's lifetime. The work of Ayonrinde et al.⁽³⁾ indicates that adolescent NAFLD is associated with parental factors in the preconception period (e.g., paternal and maternal obesity), *in utero* (e.g., gestational weight gain), and in early postnatal life (e.g., breastfeeding linked to socioeconomic status). The “baggage” of developmental programming carried through the life of offspring shows remarkable sexual dimorphism and includes different characteristics linked to adolescent NAFLD among girls and boys. Additional postnatal insults (e.g., obesogens) and comorbidities (e.g., obesity and diabetes) may further modify the risk of NAFLD in offspring and subsequent progeny with potential escalation of the liver disease phenotype.