Fetal Overnutrition and Adolescent Hepatic Fat Fraction: the Exploring Perinatal Outcomes in Children Study

Anna Bellatorre, PhD[1], Ann Scherzinger, PhD[2], Elizabeth Stamm, MD[2], Mercedes Martinez, MS[1], Brandy Ringham, PhD[3], and Dana Dabelea, MD, PhD[1]

Objective To determine if fetal overnutrition resulting from maternal obesity or gestational diabetes mellitus (GDM) is associated with increased liver fat during adolescence, adjusting for past and current metabolic risk factors.

Study design Data come from a historical prospective cohort study (Exploring Perinatal Outcomes in Children) of 254 mother-child pairs in Colorado who participated in 2 research visits at T1 (mean age 10.4, SD = 1.5 years) and at T2 (mean age 16.4, SD = 1.5 years), and had complete exposure and outcome data. Multiple linear regression was used to evaluate the effects of pre-pregnancy body mass index (BMI) and GDM on hepatic fat fraction (HFF) by magnetic resonance imaging at T2.

Results Maternal pre-pregnancy obesity (BMI 30+) was significantly associated ($\beta = 1.59$, CI = 0.66, 2.52) with increased HFF relative to mothers with normal pre-pregnancy weight (BMI <25) independent of maternal GDM and sociodemographic factors. Moreover, this association was independent of T2 and T1 metabolic risk factors (acanthosis nigricans, BMI, fasting glucose) ($\beta = 1.03$, CI = 0.10, 1.97). Prenatal GDM exposure was not associated with HFF in either unadjusted or adjusted models.

Conclusions Maternal pre-pregnancy obesity was associated with increased HFF in offspring independent of childhood and adolescent adiposity. Intervention studies are needed to test the hypothesis that maternal obesity is a modifiable risk factor for childhood fatty liver disease. *(J Pediatr 2017;■■:■■-■■).*

The intrauterine environment is critical for the growth and development of the fetus. Prior research has also demonstrated clear associations between the intrauterine environment and later metabolic risk in offspring as it relates to fetal overnutrition. Specifically, maternal pre-pregnancy overweight and obesity and gestational diabetes mellitus (GDM) during pregnancy have each been associated with increased risk of obesity, metabolic syndrome, and type 2 diabetes later in life.[1-5]

Despite interest and research in metabolic risks associated with these intrauterine exposures, there are limited data on potential associations with either adolescent liver fat accumulation or nonalcoholic fatty liver disease (NAFLD), an increasingly prevalent condition in the pediatric population.[6] Elevated visceral or organ fat, such as elevated liver fat, is associated with elevated risk of atherosclerosis,[7] type 2 diabetes mellitus,[8] and long-term liver damage.[9] NAFLD includes a spectrum of disorders, including simple steatosis, non-alcoholic steatohepatitis, inflammation and fibrosis, cirrhosis, and hepatocellular carcinoma.[10,11] NAFLD has become the leading chronic liver disease in the world, present in ~30% of adults who are usually obese in association with high-fat diets and physical inactivity.[10]

One large epidemiologic study of these exposures and NAFLD in children and adolescents,[12] the Avon Longitudinal Study of Parents and Children (ALSPAC) in the United Kingdom, reported that maternal overweight/obesity and GDM were each associated with higher levels of ultrasound assessed hepatic fat; however, when adjusted for offspring obesity, the association with maternal overweight/obesity disappeared, whereas the association of maternal GDM did not. There were also 2 similar smaller studies conducted in the US.[13,14] Using a contemporary US cohort in Colorado, we aimed to study whether maternal pre-pregnancy obesity and prenatal GDM exposure are associated with increased adolescent hepatic fat fraction (HFF) as measured by magnetic resonance imaging (MRI), a marker for fatty liver. In addition, we examined whether such associations were mediated by childhood and adolescent obesity, a marker associated with insulin-resistance and elevated glucose levels.

ALSPAC	Avon Longitudinal Study of Parents and Children
EPOCH	Exploring Perinatal Outcomes in Children
GDM	Gestational diabetes mellitus
HFF	Hepatic fat fraction
MRI	Magnetic resonance imaging
NAFLD	Nonalcoholic fatty liver disease
USS-FL	Ultrasound assessment of fatty liver

From the [1]Department of Epidemiology, University of Colorado School of Public Health; [2]Department of Radiology, University of Colorado School of Medicine; and [3]Department of Biostatistics and Informatics, University of Colorado School of Public Health, Aurora, CO

Supported by the National Institutes of Health (R01DK068001). The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.09.008

Methods

Data come from the Exploring Perinatal Outcomes in Children (EPOCH) study, a historical prospective cohort study of 604 mother-child pairs who were members of Kaiser Permanente of Colorado at the time of the child's birth.[15] The EPOCH study was designed to explore the effects of fetal overnutrition on childhood adiposity-related outcomes, with a special focus on exposure to maternal GDM and obesity. Thus, by design, the study oversampled on maternal obesity and GDM exposure. Approximately one-quarter (24.0%) of the sample youth were exposed to GDM and one-half (50.6%) of the mothers in the sample had pre-pregnancy BMI levels that were either overweight or obese prior to the start of the index pregnancy. A first EPOCH visit (T1) was conducted when youth were, on average, 10.4 years of age (SD = 1.5) during 2005-2010 (n = 604). A second visit (T2) took place during 2011-2015 when youths were on average 16.4 years (SD = 1.5) (n = 417). The Colorado Multiple Institutional Review Board approved the EPOCH study. Mothers provided written informed consent, and youth provided written assent. This report includes 254 participants who completed both T1 and T2 visits and had nonmissing exposure and outcome data (**Figure**).

The exposures of interest were mother's pre-pregnancy obesity status and GDM. Maternal weight before the last menstrual cycle preceding pregnancy (from the Kaiser Permanente of Colorado records) and measured maternal height at the first research visit were used to calculate pre-pregnancy body mass index (BMI) as weight (kg)/height (m^2). Mothers were categorized as underweight or normal (BMI ≤24.9), overweight (25.0-29.9), and obese (30.0+). All pregnant women were routinely screened for GDM at 24-28 weeks using the 2-step standard protocol.[16] We elected to combine maternal prepregnant underweight (n = 8) and normal weight (n = 120) because of too few cases of maternal pre-pregnancy underweight for separate analyses. GDM was diagnosed if glucose values exceeded 2 SD thresholds set by the National Diabetes Data Group on the 3-hour, 100 g oral glucose tolerance test.[17]

The outcome variable in this study was the HFF obtained by MRI at T2. Hepatic imaging was performed using a magnitude based, 6-echo, spoiled gradient-recalled echo sequence,[18] which allowed correction for T2* effects. HFF was calculated from the mean pixel signal intensity data, for each echo acquisition using an open source Osirix algorithm.[19] This fraction was then multiplied by 100 such that a value of 1 is equivalent to 1% HFF. An HFF of 5.56% or greater was indicative of fatty liver in adults.[20]

Both T1 and T2 included extensive study questionnaires about the adolescent's health and family contexts and the mother's health during and prior to the index pregnancy. Sociodemographic covariates included child age in years at the time of the T2 visit, child sex, child race/ethnicity with options for non-Hispanic black, Hispanic, non-Hispanic other race (non-Hispanic white reference), an indicator variable of low parent education (highest parent education high school or less = 1, more than high school = 0), and an indicator for household income in the bottom 35% of the sample ($74 999 or less = 1, $75 000+ = 0). Specific metabolic risk mediators measured at both visits included child age and sex standardized BMI scores standardized to US youth (BMIz scores), calculated using Centers for Disease Control and Prevention reference standards[21,22]; elevated fasting glucose level (≥100 vs ≤99 mg/dL) during the research visit; and presence of acanthosis nigricans, a pattern of skin texture and coloring associated with insulin resistance determined by a trained examiner.[23]

Statistical Analyses

We employed listwise deletion for complete case analyses. Of the 417 respondents who completed both visits, 254 had nonmissing covariate, exposure, and outcome data. A schematic detailing the exclusion criteria and the effects on the sample size are included in the **Figure**.

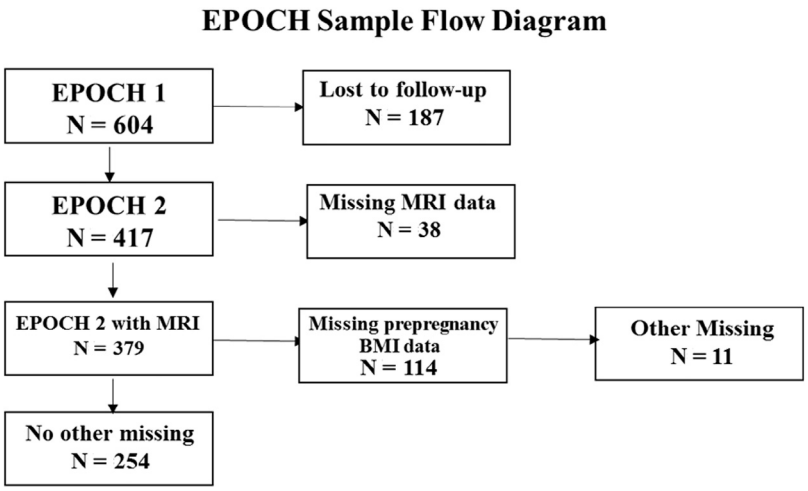

Figure. EPOCH sample inclusion flow diagram.

FLA 5.5.0 DTD ■ YMPD9445_proof ■ October 14, 2017