Retrospective Study

Association of maternal obesity and gestational diabetes mellitus with overweight/obesity and fatty liver risk in offspring

Zeng J et al. Maternal obesity and GDM and offspring status

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Abstract

BACKGROUND
Childhood obesity and fatty liver are associated with adverse outcomes such as diabetes, metabolic syndrome, and cardiovascular diseases in adulthood. It is very important to identify relevant risk factors and intervene as early as possible. At present, the relationship between maternal and offspring metabolic factors is conflicting.

AIM
To estimate the association of maternal obesity and gestational diabetes mellitus (GDM) with overweight/obesity and fatty liver risk in offspring at 8 years of age.

METHODS
The prospective study included mothers who all had a 75-g oral glucose tolerance test at 24-28 wk of gestation and whose offspring completed follow-up at 8 years of age. Offspring birth weight, sex, height, weight, and body mass index (BMI) were measured and calculated. FibroScan-502 examination with an M probe (Echosens, Paris, France) was prospectively conducted in offspring aged 8 years from the Shanghai Prenatal Cohort Study.

RESULTS
A total of 430 mother-child pairs were included in the analysis. A total of 62 (14.2%) mothers were classified as obese, and 48 (11.1%) were classified as having GDM. The mean age of the offspring at follow-up was 8 years old. Thirty-seven (8.6%) offspring were overweight, 14 (3.3%) had obesity, and 60 (14.0%) had fatty liver. The prevalence of overweight, obesity and fatty liver in offspring increased significantly across maternal BMI quartiles (all \( P < 0.05 \)).
Among offspring of mothers with GDM, 12 (25.0%) were overweight, 4 (8.3%) were obese, and 12 (25.0%) had fatty liver vs. 25 (6.5%), 10 (2.6%) and 48 (12.6%), respectively, for offspring of mothers without GDM (all \( P < 0.05 \)). In multiple logistic regression, after adjustment for variables, the OR for fatty liver in offspring was 8.26 (95% CI: 2.38-28.75) for maternal obesity and GDM.

CONCLUSION

This study showed that maternal obesity can increase the odds of overweight/obesity and fatty liver in offspring, and GDM status also increases the odds of overweight/obesity in offspring. Weight management and glycemic control before and during pregnancy need to be highlighted in primary prevention of pediatric obesity and fatty liver.

**Key Words:** Maternal obesity; Gestational diabetes mellitus; Offspring overweight/obesity; Offspring fatty liver; FibroScan

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**Core Tip:** It is very important to identify relevant risk factors of childhood obesity and fatty liver and intervene as early as possible, considering their adverse outcomes. In this work, we reported the association of maternal obesity and gestational diabetes mellitus (GDM) with overweight/obesity and fatty liver risk in offspring at 8 years of age. This study showed that maternal obesity can increase the odds of overweight/obesity and fatty liver in offspring, and GDM status also increases the odds of overweight/obesity in offspring, Weight
management and glycemic control before and during pregnancy need to be highlighted in primary prevention of pediatric obesity and fatty liver.

INTRODUCTION

With economic development and changing living and eating habits, the prevalence of obesity in children has been rapidly increasing in recent decades\(^1\). It is alarming because it is also associated with health consequences such as metabolic syndrome, diabetes, cardiovascular diseases, and even many types of cancers in adulthood\(^2,3\). The incidence of fatty liver in children is also rising, due, in part, to the increasing prevalence of childhood obesity. At present, there is still no effective noninvasive means for diagnosing fatty liver in children. Recently, some novel noninvasive techniques for the assessment of liver fat have been developed. Transient elastography (TE) is one of these new techniques based on inducing a shear wave to the liver and measuring the velocity of the wave. The device (FibroScan-502, Echosens, Paris, France) was developed using the TE technique, and controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) can be obtained simultaneously by the device in a rapid, noninvasive, reproducible, and painless way. FibroScan-502 has also been used in the assessment of liver fat and fibrosis in pediatric individuals with liver diseases, and the reference values of CAP have been studied in our previous article\(^4\).

Recent studies have suggested that maternal body mass index (BMI) is associated with the birth weight of offspring and is a risk factor for offspring obesity\(^5,6\). Gestational diabetes mellitus (GDM) is the occurrence of glucose intolerance during pregnancy and usually resolves after birth\(^7\). Meanwhile, many studies have shown that GDM can increase the incidence of impaired glucose tolerance in offspring and increase the risk of offspring obesity\(^8,9\).
Therefore, in this article, we aimed to assess whether maternal BMI and in utero exposure to GDM are associated with a long-term risk of overweight/obese and fatty liver among offspring 8 years postpartum.

MATERIALS AND METHODS

Study population

The individuals included in the prospective study were 430 maternal-child pairs from the Shanghai Prenatal Cohort Study, which is a prospective study that enrolled 1043 Han maternal-child pairs between January 2012 and December 2013 at Xinhua Hospital and International Peace Maternity and Child Hospital in Shanghai. The offspring were followed up at the age of 8 years (94 and 98 mo) with medical examinations. The exclusion criteria for the study population were as follows: (1) Non-Shanghai residents; (2) lost to follow-up; (3) missing some of the mothers' clinical information on prepregnancy and the offspring's anthropometric data; (4) mothers' medical history of diabetes (diagnosed before the index pregnancy) and other participants whose fasting glucose was ≥ 7.0 mmol/L before 12 gestational weeks; and (5) failure of FibroScan-502 measurement with an M probe. Ethics approval was obtained by the Ethics Committees (XHEC-C-2012-023). The parents of all the participating children were required to give informed consent for study participation and sign the written documents.

Clinical and laboratory data collection

All mothers' heights and weights were measured in light indoor clothing and without shoes during early pregnancy. The oral glucose tolerance test (OGTT) was conducted between 24 and 28 wk gestation among those mothers. All followed-up offspring underwent annual medical examination at the health examination center in Xinhua Hospital. Stadiometers (Seca 416 Infantmeter,
United States) were used to measure height to the nearest 0.1 cm. Digital scales (Detector 6745 Baby Scale, United States) were used to measure body weight to the nearest 0.1 kg. Participant characteristics and anthropometric indices, including age, sex, body weight, height, chest circumference, waist circumference, hip circumference and BMI, were obtained.

Following a fast of at least 6 h, all offspring underwent FibroScan-502 examination with an M-probe (3.5 MHz) (Echosens, Paris, France) by the same physician. The device estimates liver stiffness in kilopascals (kPa) and liver steatosis in decibels/meter (dB/m). CAP in dB/m and LSM in kPa were obtained simultaneously by each examination. A TE examination was considered successful when 10 valid measurements with a success rate of at least 60% were conducted and the interquartile range (IQR) was less than 30% of the median LSM value[10]. Subjects with unsuccessful examinations were excluded from the analyses.

Work definitions
Maternal obese, overweight and lean: A BMI during the early pregnancy greater than 25 kg/m² was used to define the obese population, and a BMI less than 25 kg/m² was used to define the nonobese population. The nonobese population was further divided into lean (< 23 kg/m²) and overweight (23-25 kg/m²) groups.

GDM: All mothers without diagnosed diabetes were screened for GDM by a one-step approach undergoing a 75g OGTT after fasting overnight between 24 and 28 wk’ gestation according to the guideline from Obstetrics and Gynecology Branch of Chinese Medical Association[11]. GDM was diagnosed when the glucose level that met or exceeded any of the following standards: a blood glucose value of 92, 180 or 153 mg/dL before or one or two hours after taking a 75 g glucose tolerance test, respectively.
Offspring overweight/obesity were defined by using the International Obesity Task Force age- and sex-specific cutoff points\cite{12}.

Offspring fatty liver: The offspring were considered to have fatty liver when the CAP value exceeded the normal value of 214.53 dB/m\cite{4}.

**Statistical analysis**

Continuous variables are expressed as the mean ± SD for a normal distribution and as the median ± IQR for a skewed distribution. General linear models for continuous variables were used to compare means of characteristics, and the χ² test for categorical variables was applied to compare offspring proportions across quartiles of maternal BMI during early pregnancy. We further explored the effects of maternal GDM status on such associations by a stratified analysis according to GDM status. Multivariate logistic regression models were used to examine the relationship between maternal BMI during early pregnancy and GDM status and offspring overweight/obesity status and fatty liver prevalence. Multiple logistic regression was used for continuous outcomes, and the results are reported as odds ratios (ORs) with 95% CIs. Three multivariate-adjusted models were included in these analyses. Significance tests were two tailed, and a P value < 0.05 was considered statistically significant. The data analysis for this article was generated using SAS Version 9.4.

**RESULTS**

**Participant characteristics**

A total of 513 maternal-child pairs from the Shanghai Prenatal Cohort Study were prospectively followed for 8 years. Of these individuals, 430 mothers and their offspring were included in the analysis (Figure 1).
The characteristics of participating mothers and offspring are shown in Table 1. The mean maternal age before pregnancy was 29 (4.9) years (20 to 42 years old). The mean maternal BMI was 21.55 (3.59) kg/m². A total of 62 (14.2%) mothers were classified as obese, and 48 (11.1%) were classified as having GDM. The mean birth weight of the offspring was 3.40 ± 0.48 kg and 210 (48.8%) were boys. A total of 37 (8.6%) offspring were classified as overweight, 14 (3.3%) offspring were classified as obese, and 60 (14.0%) had fatty liver (Table 1).

*Maternal BMI and the characteristics of the mothers and offspring*

Across maternal BMI quartiles, mothers in higher maternal BMI quartiles were more likely to have a greater weight and GDM. The offspring of mothers in higher maternal BMI quartiles were also more likely to have greater birth weight, BMI, waist circumference, hip circumference, chest circumference and CAP values and to be more prone to overweight/obese and fatty liver (Table 1).

*The association of maternal BMI with outcomes for offspring*

The fatty liver risk of these offspring increased progressively from the lowest to the highest quartiles of maternal BMI, with odds ratios (ORs) of 5.84 (95%CI: 0.67-50.67), 9.76 (95%CI: 1.21-78.83), and 26.3 (95%CI: 3.21-215.3), respectively, after controlling for the sex and age of the offspring (Model 1). Further adjusting for maternal age, nulliparity (Model 2), GDM status of the mothers and birth weight (Model 3) did not change the associations (Table 2).

The OR of the offspring overweight/obesity risk in the highest quartile of maternal BMI was 10.6 (95%CI: 2.17-51.76) after controlling for the sex and age of the children (Model 1) (Table 2).
Association of maternal GDM status with offspring overweight/obesity and CAP values

As shown in Table 3, mothers with GDM weighed more, had higher maternal BMIs and had a higher prevalence of maternal obesity than mothers without GDM (all $P < 0.05$). The offspring of mothers with GDM had higher BMI, chest circumference, hip circumference, and CAP values (all $P < 0.05$). Among offspring whose mothers had GDM, 4 (8.3%) were obese, compared with 10 (2.6%) offspring whose mothers did not have GDM ($P < 0.000$). However, there were no significant differences in birth weight, sex distribution, weight at follow-up, waist circumference, or E values between the offspring of mothers with and without GDM (Table 3).

The CAP values of the offspring gradually increased in the mothers with neither obesity nor GDM (163.62 ± 44.41) dB/m, GDM but no obesity (173.43 ± 34.57) dB/m, obesity but no GDM (190.73 ± 49.74) dB/m to both obesity and GDM (202.15 ± 61.55) dB/m (all $P < 0.05$) (Figure 2).

The association of maternal obesity and GDM with outcomes for offspring

Maternal obesity was positively associated with childhood fatty liver with OR 4.57 (95% CI: 1.96-10.67) and childhood overweight/obesity with OR 5.73 (95% CI: 2.18-15.10) (Model 1). Further adjustment for maternal age, nulliparity (Model 2), GDM status of the mother and birth weight (Model 3) did not change the associations (Table 4).

Maternal GDM was also positively associated with childhood overweight/obesity, with an OR of 4.70 (95% CI: 1.72-12.81) (Model 1). Additionally, further adjustment for maternal age, nulliparity (Model 2), and offspring birth weight (Model 3) did not change the associations. In addition, the association of maternal GDM with childhood fatty liver was not statistically significant, with an OR of 2.39 (95% CI: 0.91-6.29) (Model 1) (Table 4).
DISCUSSION

In this prospective birth cohort, we assessed the causal association of maternal metabolic disorders with offspring overweight/obesity and fatty liver in Han Chinese populations. This study demonstrated that high maternal BMI increased the odds of both childhood overweight/obesity and fatty liver, independent of maternal age, offspring birth weight, and childhood waist circumference at 8 years of age. Furthermore, maternal pregnancy glucose concentrations were positively correlated with offspring CAP values at school age. These two findings corroborated that the negative impacts of maternal obesity and impaired glucose metabolism on offspring livers are long-term and not merely limited to infancy.

More impressively, the negative effects of maternal obesity and impaired glucose metabolism might vary in degree. A recent cohort study based on magnetic resonance imaging found that maternal early-pregnancy glucose levels were associated with a 1.95-fold increase in odds of offspring non-alcoholic fatty liver disease (NAFLD) only among mothers of European ancestry[13]. In our study, maternal blood samples were collected in the second trimester. We observed that maternal mid-pregnancy glucose levels had only a weak relation with offspring fatty liver among Han Chinese populations, while maternal obesity was more strongly associated with offspring fatty liver than GDM.

Maternal obesity and impaired glucose metabolism have lasting impacts on offspring hepatic health through epigenetic, dietary, and metabolic factors[14,15]. A sibling comparison cohort reported that maternal weight gain was aligned with the odds of offspring obesity[16], suggesting that maternal overnutrition may be a predisposing factor for offspring metabolic dysbiosis. This conclusion was also validated in some animal models, such as macaques and mice, and
investigators found that reversing the high-fat diet to a low-fat diet during the subsequent pregnancy alleviated offspring hepatic lipid accumulation\textsuperscript{[17-19]}. In terms of mechanisms, one study demonstrated that maternal obesity might render innate immunity dysfunctional, and another study observed that maternal obesity accelerated the progression of offspring NAFLD through activation of lipogenesis and oxidative stress pathways\textsuperscript{[20,21]}.

Our observations were mutually verified with previous studies and have several differences as follows. Two studies focused on the relation between maternal factors and infant hepatic fat\textsuperscript{[22,23]}. Modi \textit{et al.}\textsuperscript{[23]} observed that increasing maternal BMI might initiate lipid accumulation in infant livers. Subsequently, Brumbaugh and colleagues reported that infants of GDM mothers had greater hepatic steatosis than infants of non-GDM mothers\textsuperscript{[22]}. In contrast, our study revealed the relatively long-term health outcomes in school-age children to corroborate that such associations might predispose children to fatty liver later in life.

Another study in obese mothers observed a positive relation with offspring ultrasound-diagnosed NAFLD during adolescence. However, ultrasound has limited power to detect mild steatosis and cannot quantify histological characteristics such as hepatic lipid content and liver stiffness. In our studies, we assessed pediatric liver pathology through TE, which is a reliable noninvasive diagnostic tool for fibrosis assessment in NAFLD\textsuperscript{[24]}. Meanwhile, a biopsy-confirmed study reported that an association between parental obesity and offspring liver fibrosis was found in Italians\textsuperscript{[25]}. As maternal impaired glucose metabolism was only related to offspring NAFLD in Europeans\textsuperscript{[13]}, the association between maternal obesity and progression of NAFLD in offspring may also differ across ethnic groups and the possible mechanisms need to be explored\textsuperscript{[26,27]}.
To the best of our knowledge, the present study is the first prospective birth cohort to assess the causal relationship between maternal metabolic dysbiosis and the odds of fatty liver in offspring. After adjustment for multiple regression models, the results were rigorous and trustworthy. Nonetheless, there are still several limitations that are worthy of discussion. First, to date, there is no widely accepted threshold of TE to detect childhood liver steatosis and fibrosis\[^{[28]}\]. We used the 95th percentile cutoff values reported in a large health check-up cohort of preschool children as a surrogate threshold for this study\[^{[4]}\]. Second, in this cohort, only 11.1% of mothers developed GDM during pregnancy, which reflected the true prevalence of GDM in the Chinese population. However, the small number of mothers with GDM might lead to type-2 statistical errors. Further nested case-control studies can address this issue and are recommended. Ultimately, single nucleotide polymorphisms of the patatin-like phospholipase domain containing 3, transmembrane 6 superfamily member 2, glucokinase regulatory protein, and several other susceptibility genes were not determined in this cohort. Further studies are needed to explore whether a predisposed genetic background mediates the influence of maternal metabolic dysbiosis on offspring NAFLD.

With the rapid spread of childhood fatty liver, it is urgent to develop preventive strategies against childhood fatty liver. In this regard, the current observations could be applied to the primary prevention of childhood fatty liver and obesity. The earliest timepoints of primary prevention of pediatric fatty liver could be before pregnancy. Weight management and glycemic control before and during pregnancy may help to promote liver and metabolic health status in children. Furthermore, lifestyle intervention before pregnancy is worth further investigation.

CONCLUSION
In this study, maternal obesity increased the odds of both fatty liver and obesity in offspring, independent of maternal age, GDM status and offspring birth weight at 8 years of age. On another note, the association between maternal GDM and childhood fatty liver trended toward significance in the Chinese population, and this association needs to be confirmed in studies with larger sample sizes. To prevent these intergenerational predisposing factors, weight management and glycemic control before and during pregnancy need to be highlighted for primary prevention of pediatric fatty liver.
## ORIGINALITY REPORT

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