

ORIGINAL RESEARCH ARTICLE

High maternal blood lipid levels during early pregnancy are associated with increased risk of congenital heart disease in offspring

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Abstract

Introduction: This study aimed to investigate whether maternal blood lipid levels during early pregnancy are associated with the occurrence of congenital heart disease (CHD) in their offspring.

Material and methods: In this single-center case-control study, mothers of offspring with CHD ($n = 230$) and without CHD ($n = 381$) were included. Maternal lipid levels were determined on fasting blood samples taken in the first trimester. Relevant demographic and clinical data were extracted from the medical records. Maternal lipid profile was compared between the two groups, and regression analysis was performed to evaluate the association between lipid profile and CHD risk in offspring.

Results: Compared with the control group, levels of triglyceride, apolipoprotein-A1, and apolipoprotein-B in early pregnancy were significantly higher in the CHD group. Multivariate analyses showed that triglyceride (odds ratio [OR] 2.46, 95% CI 1.62–3.73, $p < 0.01$), total/high-density lipoprotein cholesterol (OR 2.10, 95% CI 1.07–4.13, $p = 0.03$), and apolipoprotein-A1 (OR 2.73, 95% CI 1.16–6.40, $p = 0.02$) were positively associated with CHD risk in offspring.

Conclusions: Elevated maternal lipid profile was associated with increased risk of CHD in offspring.

KEYWORDS

congenital heart defect, early pregnancy, maternal lipid profile, pregnancy, risk factor

Abbreviations: Apo-A1, apolipoprotein-A1; Apo-B, apolipoprotein-B; BMI, body mass index; CHD, congenital heart disease; HbA1c, hemoglobin A1c; Hcy, homocysteine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Li Cao and Yan Du contributed equally to this work.

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1 | INTRODUCTION

Worldwide, congenital heart disease (CHD), with an incidence of 9.1‰ among live births, is the major form of birth defect and the leading cause of childhood mortality.¹ The occurrence of CHD is caused by many factors. About 15% of CHD have genetic predisposition, but most CHD cases are the result of interactions among multiple factors.²

With the improvement in living standards and an increasing number of women with advanced maternal age, there is an increase in the prevalence of chronic metabolic diseases, such as obesity, diabetes, hypertension, and hyperlipidemia, among pregnant women. Previous research has suggested that an abnormal maternal lipid profile is associated with elevated risk of CHD in offspring.^{3,4} However, in one study the maternal lipid levels were determined at around 16 months after the index pregnancy,³ whereas most of the congenital anomalies develop during organogenesis (first trimester of pregnancy). Another study tested maternal triglyceride (TG) levels during early pregnancy, but only limited cases of CHD were included.⁴ In contrast, a large case-control study based on the multicenter population-based National Birth Defects Prevention Study reported that maternal periconceptional dietary fat intake did not increase the odds of CHD after adjusting for total energy intake.⁵ However, the food-frequency questionnaire, which is used to assess nutrient intake during the year before pregnancy, was completed at an average of 11 months after delivery.⁵ It remains controversial whether maternal lipid profile is associated with CHD risk in offspring. So far, the majority of the research has used food-frequency questionnaires to assess energy intake. In addition, retrospective studies are hampered by recall biases. To the best of our knowledge, few studies with an adequate sample size have looked into the association between the maternal lipid profile at early pregnancy and CHD risk in the offspring. Therefore, we conducted this study to investigate whether an abnormal maternal lipid profile during the first weeks of pregnancy was associated with CHD in the offspring, to provide some evidence for developing possible intervention strategies.

2 | MATERIAL AND METHODS

2.1 | Study population

This case-control study was conducted at the Obstetrics and Gynecology Hospital of Fudan University in Shanghai, China. Cases were mothers pregnant with a fetus with CHD between August 2015 and December 2018. Exclusion criteria were: known consanguinity, abnormal or unknown genetic testing results, family history of CHD, incomplete information on the mother-child pair, and intake of any lipid-lowering agents before sample collection. There were 54 864 registered pregnant women during the study period at our hospital, including 443 women pregnant with a fetus with CHD (a prevalence of 8.07‰), 24 of which had abnormal genetic testing results. In 92 cases, pregnancies were terminated before 28 weeks of

Key message

Abnormal maternal lipid profile during organogenesis (first trimester of pregnancy) may be associated with elevated risk of congenital heart disease in offspring. Investigating the association of maternal lipid profile with congenital heart disease risk may aid in developing intervention strategies.

pregnancy without previous invasive diagnostic procedures. Eight cases had a family history of CHD, and two cases did not respond to follow-up phone interview and were not included. In addition, we further excluded 54 cases of persistent left superior vena cava, 23 cases of right aortic arch, and 10 cases of aberrant right subclavian artery because they are classified as variations of normality. Controls were women giving birth to healthy infants during the same period of time, and were matched based on gestational week at the first prenatal examination of the cases. Initially 419 controls were selected, after further careful investigation of medical records, three of the controls had a family history of CHD, 23 had their blood test performed after the 14th week of gestation, and 12 controls used lipid-altering medication, and so were excluded. Finally, a total of 230 cases and 381 controls were included in the study (Figure 1).

Data regarding clinical information, ultrasound examination, genetic testing, and pathological results were extracted from electronic medical records. The following variables were collected: maternal age, gestational week, parity, sex of the child, weight and height before pregnancy, method of conception, folic acid, vitamin B12, thyroid abnormality, homocysteine (Hcy), triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), free fatty acid, Apolipoprotein-A1 (Apo-A1), Apolipoprotein-B (Apo-B), fasting blood glucose, and hemoglobin A1c (HbA1c). Body mass index (BMI) was calculated as weight/height².

2.2 | Perinatal outcome

Pregnant women who came to the hospital for their first prenatal examination at 8–14 weeks of gestation were asked to complete basic information, and fasting blood was drawn for biochemical examination. At 20–24 weeks of gestation an ultrasound examination was performed to screen for fetal abnormalities. Fetal heart abnormalities were evaluated by cardiac screening examination according to the 2013 International Society of Ultrasound in Obstetrics & Gynecology Practice Guidelines.⁶ After delivery, all newborns underwent routine clinical examination, and screening for CHD was performed using oxyhemoglobin saturation monitoring. Cardiac auscultation was performed daily by the neonatologist until discharge from the hospital. If neonatal CHD was suspected, neonatal echocardiography was

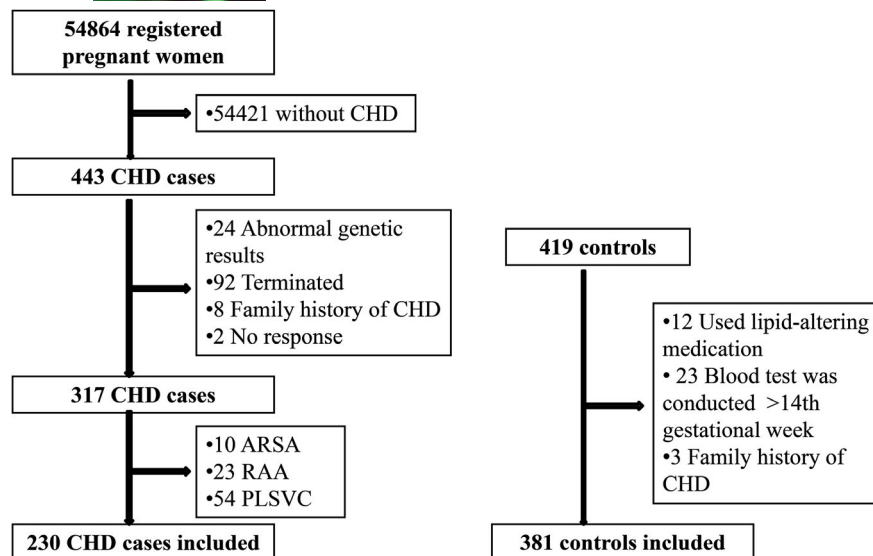


FIGURE 1 Flow chart of the study population. Abbreviations: ARSA, aberrant right subclavian artery; CHD, congenital heart disease; PLSVC, persistent left superior vena cava; RAA, right aortic arch

performed. The diagnosis of CHD before and after birth was mainly confirmed by echocardiography and/or autopsy.

When fetal CHD was suspected on screening, further detailed ultrasonographic examination was performed by senior sonologists. If the diagnosis was confirmed, amniocentesis was performed for karyotyping and human whole-genome single nucleotide polymorphism genotyping was carried out, after counseling, to exclude chromosomal abnormalities. For those who did not undergo prenatal invasive diagnostic procedures, general condition and clinical signs of the newborns were observed by neonatal pediatricians. At the same time, a family history of neonates was considered.

Classification of CHD severity was based on previous definitions.⁷ In general, we combined critical cases (defects causing death or needing intervention before age 28 days) and serious cases (defects requiring intervention before age 1 year) of CHD as severe CHD, and significant cases (defects persisting beyond age 6 months, but not classified as critical or serious) and non-significant cases (defects not physically appreciable and not persisting after age 6 months) as mild CHD. For combinations of cardiac defects, the major diagnosis was based on either the most hemodynamically significant structural anomaly or the one requiring the earliest intervention.

2.3 | Biochemical analyses

Fifteen milliliters of fasting peripheral blood samples were collected between 8 and 14 weeks of gestation. Samples were collected and allowed to clot for 30 minutes before centrifugation at 1000 *g* for 5 min. All fasting blood samples were processed within 2 hours of collection.

TG, TC, HDL-C, LDL-C, free fatty acid, Apo-A1, Apo-B, and fasting blood glucose were analyzed by an automatic biochemical analyzer (Hitachi 7180, WAKO) using commercially available kits. TG and TC were determined by the cholesterol oxidase method (WAKO), HDL-C and LDL-C were tested by the direct assay method

(Shanghai Beijia Biochemistry Reagents Co., Ltd), Apo-A1 and Apo-B were tested using the immune transmission turbidity method (Shanghai Beijia Biochemistry Reagents Co., Ltd), and free fatty acid was tested using the enzyme peroxidase end-point method (DiaSys Diagnostic). Blood glucose reagent (hexokinase method) was provided by the Japan Wako Company. TOSOH HLC-723G8 automatic glycosylated hemoglobin analyzer and original matching reagents (high-performance liquid chromatography, TOSOH Co., Ltd) were used to detect HbA1c. Folic acid and vitamin B12 were measured using the Architect i2000chemiluminescence immunoassay analyzer. Serum Hcy measurements were carried out by Liquid Chromatography Coupled to Tandem Mass Spectrometry (LC/MS/MS) using an API 3000 LC/MS/MS system (Applied Biosystems). Inter-assay coefficients of variation were <10% for all these assays.

2.4 | Statistical analyses

Differences between groups were tested using independent sample Student's *t* test for normally distributed variables and Mann-Whitney *U* test to compare skewed variables. Kruskal-Wallis test was performed to compare more than two groups. Chi-squared test or Fisher's exact test was used to compare proportions of discrete nominal variables between case and control groups as appropriate. Univariate logistic regression was used to calculate the odds ratios (ORs) and corresponding 95% CIs to estimate the risk of CHD. In the multivariable logistic regression analyses, factors considered as confounders (age, BMI, parity, gestational week, sex of the child, multiple birth, HbA1c, vitamin B12, folic acid, and Hcy) according to univariate analysis results as well as previous literatures³ were added into the model for adjustment to determine whether lipid biomarkers independently associated with CHD risk. All significance tests were two sided; a *p* value of <0.05 was considered statistically significant. Statistical analyses were conducted using STATA version 16.0 (StataCorp.).

2.5 | Ethical approval

The study protocol was approved by the institutional review board of the Obstetrics and Gynecology Hospital of Fudan University (Reference number: kyy2015-15; date of approval: April 14, 2015).

Written informed consent was obtained from all mothers.

3 | RESULTS

3.1 | General characteristics of the study population

Table 1 presents the general characteristics of the study population. In our study population, no women had reported smoking or alcohol intake periconceptionally or during early pregnancy. In general,

maternal age of the CHD mother was slightly older compared with the control group. Most of the women were within the normal BMI range. Gestational weeks and BMI were comparable between cases and controls. More mothers with CHD infants were pregnant through assisted conception compared with controls. There were no differences for the sex of the child and parity.

There were 48/230 (20.9%) infants with severe CHD and 182/230 (79.1%) infants with mild CHD. Of these, 42 cases of severe CHD and 33 cases of mild CHD were diagnosed prenatally. All suspected cases during pregnancy had undergone neonatal echocardiography. During the prenatal screening, we missed six fetuses with major CHD, including two cases of tetralogy of Fallot, two cases of total anomalous pulmonary venous drainage, one case of coarctation of the aorta, and one case of transposition of the great arteries. Detailed information on CHD subtypes are presented in Table 2.

TABLE 1 Baseline characteristics of mothers pregnant with a fetus with congenital heart disease and control mothers

	CHD group (n = 230)	Control group (n = 381)	p
Maternal age (years) ^a (median, range)	31 (20–42)	30 (21–43)	0.02
Gestational week at blood drawing ^a (median, range)	11.4 (8.3–13.5)	11.4 (8.0–13.2)	0.95
Parity (n, %)			0.02
Nullipara	183 (79.6%)	270 (71.1%)	
Multipara	47 (20.4%)	110 (28.9%)	
Sex of the child			0.52
Males	114 (49.6%)	199 (52.2%)	
Females	116 (50.4%)	182 (47.8%)	
Multiple birth			<0.001
Yes	30 (13.0%)	2 (0.5%)	
No	200 (87.0%)	379 (99.5%)	
BMI ^a , kg/m ² (median, range)	21.03 (14.36–33.25)	20.83 (14.83–38.53)	0.29
BMI < 18.5	30 (13.0%)	58 (15.2%)	0.55
18.5 ≤ BMI < 24	160 (69.6%)	272 (71.4%)	
24 ≤ BMI < 28	35 (15.2%)	44 (11.5%)	
BMI ≥ 28	5 (2.2%)	7 (1.8%)	
Gestational diabetes mellitus (n, %)			<0.001
Yes	34 (14.8%)	21 (5.5%)	
No	196 (85.2%)	360 (94.5%)	
Thyroid abnormality (n, %)			0.19
Hypothyroidism	14 (6.1%)	19 (5.0%)	
Hyperthyroidism	4 (1.7%)	6 (1.6%)	
Thyroid inflammation	8 (3.5%)	29 (7.6%)	
Normal	204 (88.7%)	327 (85.8%)	
Pregnant through assisted conception (n, %)			<0.001
No	192 (83.5%)	369 (96.9%)	
Yes	38 (16.5%)	12 (3.1%)	

Abbreviations: BMI, body mass index; CHD, congenital heart disease; SD, standard deviation.

^aMann–Whitney *U* test.

TABLE 2 Number and percentage of congenital heart disease subtypes

CHD subtypes	N	%
Ventricular septal defect (VSD)	140	44.2%
Pulmonary stenosis (PS)	27	8.5%
Tetralogy of Fallot (TOF)	17	5.4%
Coarctation of the aorta (COA)	5	1.6%
Coronary arterial fistula (CAF)	5	1.6%
Transposition of the great arteries (TGA)	4	1.3%
Hypoplastic right heart(HRH)	4	1.3%
Total anomalous pulmonary venous drainage (TAPVD)	3	0.9%
Double aortic arch (DAA)	3	0.9%
Atrioventricular septal defect (AVSD)	2	0.6%
Tricuspid regurgitation (TR)	2	0.6%
Hypoplastic left heart(HLH)	1	0.3%
Double outlet right ventricle (DORV)	1	0.3%
Ebstein's anomaly	1	0.3%
Bicuspid aortic valve (BAV)	1	0.3%
Complex congenital heart disease	14	4.4%
Total	230	100%

Abbreviation: CHD, congenital heart disease.

TABLE 3 Biomarkers in blood of mothers pregnant with fetuses with congenital heart disease and control mothers in the first trimester of pregnancy

	CHD group (n = 230)	Control group (n = 381)	Reference values ^a	p
Total cholesterol, median (range), mmol/L	4.41 (2.92–6.28)	4.36 (2.58–8.21)	3.10–5.69 mmol/L	0.70
Triglycerides, median (range), mmol/L	1.35 (0.50–3.81)	1.15 (0.44–2.84)	<1.70 mmol/L	<0.0001
Free fatty acids, median (range), mmol/L	0.53 (0.12–1.20) ^a	0.50 (0.10–1.24)	0.10–0.45 mmol/L	0.06
HDL-cholesterol, ^e mean ± SD, mmol/L	1.01 ± 0.19	1.01 ± 0.17	0.80–2.35 mmol/L	0.99
LDL-cholesterol, ^e mean ± SD, mmol/L	2.77 ± 0.49	2.79 ± 0.39	<3.12 mmol/L	0.35
Total/HDL-cholesterol, median (range)	4.43 (3.61–6.64)	4.45 (3.75–5.08)		0.46
Apolipoprotein A-1, median (range), g/L	1.19 (0.54–2.23)	1.13 (0.70–1.78)	1.00–1.60 g/L	0.01
Apolipoprotein B, median (range), g/L	0.78 (0.48–1.29)	0.75 (0.46–2.79)	0.60–1.10 g/L	0.01
Apolipoprotein B/A-1, median (range)	0.67 (0.30–1.65)	0.65 (0.33–2.71)		0.85
HbA1c, median (range), %	5.0 (3.9–5.8)	5.0 (4.0–15.8)	≤6.5%	0.57
Blood glucose, ^e mean ± SD, mmol/L	4.49 ± 0.38 ^c	4.49 ± 0.34	<5.1 mmol/L	0.94
Vitamin B12, median (range), pg/mL	489 (190–1450)	480.50 (13.90–2000.00) ^d	187–883 pg/ml	0.74
Vitamin D, mean ± SD, ng/mL	19.10 (4.50–43.00)	16.90 (5.20–42.60)	9.5–55.5 ng/ml	<0.0001
Folate, median (range), ng/mL	16.10 (3.80–24.36)	16.30 (4.70–20.00)	3.1–20.5 ng/ml	0.67
Total homocysteine, ^e mean ± SD, μmol/L	7.55 ± 2.29	6.93 ± 1.90	5–15 μmol/L	0.003

Abbreviations: CHD, congenital heart disease; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

^aReference values according to the Clinical Chemistry laboratory of the Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China. Values are means (p5–95).

^bN = 189.

^cN = 229.

^dN = 380.

^eIndependent t test.

Table 3 presents blood biomarkers in the total group. Levels of TG, Apo-A1, and Apo-B were significantly higher in the case group than the control group (all $p < 0.05$). There were no significant differences of HbA1c and fasting blood glucose levels between the two groups. No difference was observed for folate level between the two groups, but the Hcy level was significantly higher in the case group ($p = 0.003$) and the vitamin D level was significantly higher in the CHD group ($p < 0.0001$).

3.2 | Association between maternal blood lipid profile and CHD risk in offspring

After adjustment for potential confounders, we observed that a maternal lipid profile of high TG, Apo-A1, and TC/HDL-C levels in early pregnancy was associated with an increased risk of CHD in offspring. Each lipid biomarker was associated with an almost twofold increased risk of CHD, independent of HbA1c and Hcy (Table 4).

3.3 | Subgroup analysis

We further stratified the case group based on the severity of CHD. Compared with the control group, the levels of TG, Apo-A1, and

TABLE 4 Associations between maternal lipids and total homocysteine as continuous variables and congenital heart disease risk

	Crude OR (95% CI), <i>p</i>	Model 1: Adjusted OR (95% CI), <i>p</i>	Model 2: Adjusted OR (95% CI), <i>p</i>
Total cholesterol	1.06 (0.83–1.35), 0.66	0.93 (0.71–1.22), 0.61	0.88 (0.67–1.16), 0.37
Triglycerides	2.73 (1.90–3.94), <0.01	2.43 (1.61–3.67), <0.01	2.46 (1.62–3.73), <0.01
Free fatty acids	2.28 (0.88–5.88), 0.09	1.55 (0.55–4.35), 0.41	1.25 (0.44–3.58), 0.68
HDL-cholesterol	1.00 (0.40–2.51), 0.99	0.59 (0.21–1.67), 0.33	0.51 (0.18–1.45), 0.21
LDL-cholesterol	1.22 (0.83–1.79), 0.32	1.06 (0.70–1.61), 0.79	1.05 (0.69–1.60), 0.81
Total/HDL-cholesterol	1.87 (1.02–3.44), 0.04	2.15 (1.09–4.23), 0.03	2.10 (1.07–4.13), 0.03
Apolipoprotein-A1	3.31 (1.55–7.12), <0.01	3.19 (1.37–7.41), 0.01	2.73 (1.16–6.40), 0.02
Apolipoprotein-B	3.42 (1.12–10.45), 0.03	1.90 (0.61–5.88), 0.27	1.90 (0.61–5.90), 0.27
Apolipoprotein-B/A1	1.28 (0.52–3.15), 0.59	1.02 (0.38–2.75), 0.98	1.15 (0.43–3.10), 0.78

Abbreviations: CHD, congenital heart disease; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Model 1: adjusted for age, body mass index, parity, gestational week, sex of the child, multiple birth, HbA1c, vitamin B12, folic acid.

Model 2: adjusted for age, body mass index, parity, gestational week, sex of the child, multiple birth, HbA1c, vitamin B12, folic acid, homocysteine.

TABLE 5 Lipid biomarkers among the mothers pregnant with fetuses with mild and severe congenital heart disease compared with control mothers

	Mild CHD cases (n = 182), median (range)	Severe CHD cases (n = 48), median (range)	Control group (n = 381), median (range)	<i>p</i> ^c	<i>p</i> ^b	<i>p</i> ^c	<i>p</i> ^d
Total cholesterol, mmol/L	4.44 (2.92–6.07)	4.16 (3.05–6.28)	4.36 (2.58–8.21)	0.11	0.24	0.12	0.05
Triglycerides, mmol/L	1.38 (0.50–3.53)	1.21 (0.52–3.81)	1.15 (0.44–2.84)	<0.001	<0.001	0.17	0.13
Free fatty acids, mmol/L	0.54 (0.12–1.20)	0.53 (0.28–1.05)	0.50 (0.10–1.24)	0.17	0.10	0.25	0.84
HDL-cholesterol, mmol/L	1.00 (0.56–1.56)	0.97 (0.63–1.59)	1.00 (0.52–1.82)	0.35	0.66	0.19	0.17
LDL-cholesterol, mmol/L	2.76 (1.46–4.05)	2.66 (1.20–3.67)	2.69 (0.81–5.21)	0.08	0.045	0.36	0.13
Total/HDL-cholesterol	4.43 (3.69–6.64)	4.44 (3.61–5.55)	4.45 (3.75–5.08)	0.71	0.41	0.92	0.72
Apolipoprotein A1, g/L	1.19 (0.63–2.23)	1.19 (0.54–1.92)	1.13 (0.70–1.78)	0.049	0.02	0.23	0.88
Apolipoprotein B, g/L	0.78 (0.51–1.14)	0.72 (0.48–1.29)	0.75 (0.46–2.79)	0.004	0.001	0.86	0.12
Apolipoprotein B/A1	0.67 (0.35–1.29)	0.66 (0.30–1.65)	0.65 (0.33–2.71)	0.69	0.63	0.55	0.40

Abbreviations: CHD, congenital heart disease; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

b,c,d: Bonferroni correction, *p* < 0.0167 (0.05/3).

^aKruskal–Wallis test, median (range).

^bMild vs Control.

^cSevere vs Control.

^dMild vs Severe.

Apo-B were significantly elevated in the mild CHD group after Bonferroni correction (*p* < 0.0167 for all). No association was observed between the lipid profile and severe CHD group (Table 5).

4 | DISCUSSION

The current study found that elevated levels of Apo-A1, TG, and TC/HDL-C in the first trimester of pregnancy were significantly associated with increased risk of CHD in offspring. The significant

associations remained after adjusting for various possible confounders. Lipids are essential for the synthesis of cell membranes. Moreover, lipids act as ligands for the receptors and transcription factors involved in intracellular signaling processes and the regulation of gene expression.⁸

The main functions of TG are to supply and store energy, and to fix and protect the internal organs. A pilot study from India has reported that a high level of maternal TG was associated with increased risk of neural tube defects.⁹ A cohort study from Amsterdam found that both decreased and elevated TG levels in

early pregnancy were associated with increased risk of congenital anomalies, especially cardiovascular congenital anomalies, in offspring.⁴ In contrast, another study from the Netherlands did not find an association between maternal TG level and CHD risk in offspring; however, the blood samples used were taken 16 months after the index pregnancy.³ In our study, we found a significant association between maternal TG level and CHD risk in offspring. After adjusting for covariates, the significant association still existed, with an adjusted OR of 2.46. The inconsistent results from different studies may be explained by different time windows when the blood was drawn. In addition, these studies were conducted in different populations.

As a major apolipoprotein of HDL-C, Apo-A1 plays a role in regulating reverse cholesterol transport and HDL particle metabolism. Therefore, Apo-A1 may have a significant effect on the maternal lipid profile during pregnancy, and may play a supportive role in regulating maternal and fetal cholesterol homeostasis.¹⁰ Apo-B and Apo-B/Apo-A1 can predict atherosclerotic lipid disorders and cardiovascular risk in adults. A previous study has reported that Apo-B as well as Apo-B/Apo-A1 are associated with an almost twofold increased CHD risk,³ while in another study, the association of Apo-B and Apo-A1 with congenital anomalies in offspring was absent.⁴ In our study, we found that the maternal levels of Apo-B and Apo-A1 were significantly higher in the CHD group compared with the control group, and after adjusting for possible confounders, the association between Apo-A1 and CHD risk in offspring remained. During the early development stage, transfer of maternal cholesterol through the placenta is crucial when the fetus cannot synthesize its own cholesterol, and changes in maternal Apo-A1 level during early pregnancy may affect the transport of cholesterol, and so affect fetal development.

Cholesterol is an important nutrient for normal fetal development. In addition, it is an essential component of cell membranes and steroid hormones. Previous research has reported a trend of increased microcephaly risk among neonates of mothers with low serum cholesterol.¹¹ A large registry-based study from Norway has suggested that women with familial hypercholesterolemia do not appear to have a higher risk of preterm delivery or of having infants with congenital malformations than women in general.¹² In contrast, a study from the Netherlands reported that abnormal cholesterol, LDL-C, and TC/HDL-C was associated with increased risk of CHD in offspring.³ Our study did not observe significant differences of cholesterol level between the cases and controls, but TC/HDL-C was significantly higher in the case group. After adjusting for possible confounders, maternal TC/HDL-C remained a risk factor for CHD in offspring. A meta-analysis including 61 prospective observational studies has suggested that TC/HDL-C is a very strong predictor of ischemic heart disease mortality, which is more informative than TC.¹³

Dietary structures vary greatly among different populations. There is more carbohydrate consumption in the East, but more meat consumption in the West. A cross-sectional study from Korea reported that TG level was positively associated with carbohydrate indices. However, TC, LDL-C, and HDL-C levels were not significantly associated with carbohydrate intake overall.¹⁴ Compared with

white European pregnant women, pregnant South Asian women had higher gestational fasting and post-load glucose levels and increased risk of gestational diabetes despite lower BMI.¹⁵ Therefore, studies from different regions and populations yielding inconsistent results may be explained by environmental as well as genetic factors. However, our results, as well as other studies, have indicated that even a slightly disordered maternal lipid profile during the sensitive and critical period of early embryonic development may result in abnormal cardiac development in the offspring.⁴

In the current study, maternal levels of folate were relatively high and were comparable between cases and controls. Genetic and biochemical studies have shown that the preventive effect of folate is through lowering the level of hyperhomocysteinemia, which is a biomarker of oxidative stress and can induce the occurrence of CHD.^{16,17} We found that the Hcy level was significantly elevated in the case group, indicating that oxidative stress may have increased in mothers of offspring with CHD.

The mechanism of CHD development remains largely elusive, and is regulated by both genetic and environmental factors. Our analysis has suggested that multiple birth, GDM, and assisted conception are strong predictors of CHD in offspring (Table 1), which is consistent with previous research. Twin birth is associated with a higher risk of CHD than single birth, with monozygotic twins having an even higher risk.¹⁸ Although the exact mechanism remains unclear, studies have suggested that both gestational diabetes mellitus and pre-gestational diabetes mellitus are associated with increased CHD risk in offspring.¹⁹ There is evidence that assisted reproductive technologies may increase the risk of CHD, particularly mild CHD, in offspring.²⁰ It is speculated that compared with natural pregnancy, epigenetic modification in genes during assisted reproductive technologies may cause differential gene expression in fetuses and infants, contributing to adverse perinatal outcomes.²¹ The current study found that increased levels of maternal lipids in early pregnancy (first trimester) were mainly associated with mild CHD. Whereas for severe CHD, no association was observed, which should be stronger. However, we only had 48 severe cases, so our study did not have enough power. Future studies are needed to investigate the association and to clarify the underlying mechanism.

One limitation of the current study is that it is a single-center case-control study, information was extracted from medical records, and variables such as ethnicity, educational level, and socioeconomic status were missing. We did not collect paternal information either. However, both epidemiological and laboratory studies have suggested that paternal age, environmental factors, and alcohol intake may influence the risk of birth defects in offspring.²² In addition, most cases included in the current study are mild CHD. We did not have a large enough sample size to further analyze the association between lipid profile and different subtypes of CHD with sufficient statistical power. Furthermore, 92 pregnancies were terminated without an invasive diagnostic procedure and were excluded from the analysis, which may introduce selection bias. Previous studies have shown that a better quality maternal diet is associated with

a lower rate of some conotruncal and atrial septal heart defects.²³ There are differences in CHD occurrence in different populations, as well as variations in maternal metabolites. Therefore, international multicenter studies are needed to elucidate specific relation between maternal metabolites and CHD in offspring.

5 | CONCLUSION

Our study reported that mild dyslipidemia in early pregnancy was closely associated with the occurrence of CHD in offspring. In combination with previous research, it is possible that lipid metabolism in early pregnancy may influence the outcome of pregnancy. However, the association needs to be further investigated by large prospective studies as well as mechanistic studies to establish its causality. However, prevention is the key. Based on current knowledge, it is helpful to encourage lifestyle intervention strategies such as regular exercise, healthy diet, and weight control that may improve the lipid profile in the preconception period and early pregnancy, which may achieve better health in offspring.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

LC designed the study, collected data, and wrote the manuscript; YD performed statistical analyses, composed figures and tables, and wrote the manuscript; MZ analyzed data and constructed tables; FW performed genetic testing; JZ and YR interpreted results, and critically revised the manuscript; YG conceived and designed study, and critically revised the manuscript.

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