Received: 20 May 2022 | Revised: 12 November 2022 | Accepted: 5 December 2022

DOI: 10.1002/bdr2.2139

Birth Defects Research | Society for Birth Defects Research & Prevention | WILEY

RESEARCH ARTICLE

Maternal first trimester metabolic profile in pregnancies with transposition of the great arteries

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Funding information
Academy of Finland; Finnish Foundation for Pediatric Research; University of Helsinki; Pediatric Research Center of the Hospital District of Helsinki and Uusimaa (HUS); Finnish Medical Foundation

Abstract

Background: Higher maternal body mass index (BMI) and abnormal glucose metabolism during early pregnancy are associated with congenital heart defects in the offspring, but the exact mechanisms are unknown.

Methods: We evaluated the association between maternal first trimester metabolic profile and transposition of the great arteries (TGA) in the offspring in a matched case–control study with 100 TGA mothers and 200 controls born in Finland during 2004–2014. Cases and controls were matched by birth year, child sex, and maternal age and BMI. Serum samples collected between 10- and 14-weeks of gestation were analyzed for 73 metabolic measures. Conditional logistic regression was used to assess the risk for TGA in the offspring, and a subgroup analysis among mothers with high BMI was conducted.

Results: Higher concentrations of four subtypes of extremely large very-low-density lipoprotein (VLDL) particles and one of large VLDL particles were observed in TGA mothers. This finding did not reach statistical significance after multiple testing correction. The pooled odds ratio (OR) of the all metabolic variables was slightly higher in TGA mothers in the subgroup with maternal BMI over 25 (OR 1.25) and significantly higher in the subgroup with maternal BMI over 30 (OR 1.95) compared to the original population (OR 1.18).

Conclusions: Our findings indicate that an abnormal maternal early pregnancy metabolic profile might be associated with TGA in the offspring, especially in obese mothers. A trend indicating altered VLDL subtype composition in TGA pregnancies warrants further research.

KEYWORDS

congenital heart defect, epigenetics, fetal metabolism, maternal metabolism, maternal obesity, transposition of the great arteries, women of childbearing age

1 | INTRODUCTION

Congenital heart defects (CHD) are the most common congenital anomalies, and transposition of the great arteries (TGA) is one of the most frequent cyanotic CHD in neonates. The birth prevalence of TGA is approximately 2–3 per 10,000 (Hautala et al., 2021; Liu et al., 2019). More than 50% of infants will die by the first month of life and 89.3% in the first year if TGA is left untreated (Liebman et al., 1969), but when treated, this condition has a good prognosis: in a single-center South Korean study the survival rate of operated patients was 96% at 20 years (Choi et al., 2010).

Maternal metabolic conditions, such as diabetes (Becerra et al., 1990; Rowland et al., 1973), higher hemoglobin A1C (Lisowski et al., 2010), and elevated random plasma glucose values in the first trimester in mothers without diabetes (Helle et al., 2018) have been associated with an increased risk for CHD, including TGA, in the offspring. The risk is increased even in diabetic mothers with good glycaemic control (Evers et al., 2004). Previous studies have further consistently reported maternal overweight as a risk factor for offspring's CHD, including TGA (Hautala et al., 2019), and this risk increases along with the severity of obesity (Brite et al., 2014; Cai et al., 2014; Persson et al., 2017, 2019).

The pathophysiological mechanisms leading to abnormal cardiac development in pregnancies affected by maternal obesity require further research. Pre-pregnancy obesity is known to increase the risk for gestational diabetes mellitus (GDM) (Torloni et al., 2009). Abnormal glucose metabolism does not, however, entirely explain the increased risk for CHD in the offspring of obese mothers (Brite et al., 2014). The causal relationship and increased risk are likely to be multifactorial including different cardiometabolic factors and epigenetic mechanisms. Only a few studies have previously assessed the metabolomic profile of maternal blood during the first trimester of pregnancy, which reflects the metabolic circumstances at the time of cardiac morphogenesis.

The aim of our study was to further elucidate the association between maternal metabolic risk factors and the risk for CHD in the offspring. We compared a panel of first-trimester metabolic markers among women who delivered a child with TGA and women who delivered a healthy child in a setting of a matched case–control study.

2 | METHODS

All expectant mothers in Finland are entitled to a follow-up at an outpatient maternity clinic. In conjunction with their first visit to the clinic, the expectant mothers are screened for infectious diseases: syphilis, HIV and hepatitis B. These screening serum samples collected over the years 1983–2016 (Finnish Maternity Cohort) were deposited at Biobank Borealis if the mother consented to this (Biobank Borealis, n.d.).

From a national cohort of all live-born infants with simple d-TGA (TGA ± small ventricular septal defect, $n = 127$) born in Finland during 2004–2014 (Hautala et al., 2020), we identified live-born cases for whom register data and Biobank serum samples were available ($n = 100$). Each case was matched with two healthy controls ($n = 200$) according to the sex of the child, year of birth, and the age and the body mass index (BMI) of the mother as well as Biobank sample availability. From the controls meeting the matching criteria, those two controls born chronologically closest to the cases were chosen.

The background data was collected from the Medical Birth Register maintained by the Finnish Institute for Health and Welfare. Maternal BMI was calculated from the register data based on maternal pre-pregnancy weight and height.

The maternal screening serum samples were requested from the Biobank Borealis and analyzed using an automated high-throughput serum nuclear magnetic resonance (NMR) metabolomics platform (Soininen et al., 2015).

The characteristics of the study population are presented as percentages and frequencies (categorical variables) or as medians and interquartile ranges (IQRs) or means and standard deviations (SD) depending on the normality of the variable (continuous variables). Birth weight, length, and head circumference were measured in grams and centimeters, and then converted into SD units (i.e., deviation from Finnish general population mean accounting for plurality and parity (Sankilampi et al., 2013)). Maternal smoking was defined as any smoking during pregnancy including those who ceased smoking during the first trimester of pregnancy.

The metabolic measures are absolute concentration units (i.e., millimoles per liter) of different magnitudes. The normality of the distributions were analyzed by visual inspection of histograms and using skewness as a test of normality. The measures were log-transformed when skewed (skewness >1) and scaled to standardized values (Z-score) prior to analysis to allow comparison of associations across metabolites. We excluded one case and its controls and one control because of outliers exceeding the Z-score ± 5 in more than one variable. Variables potentially affected by the sensitivity of the sample handling process and 0-values were excluded. Analysis was undertaken on 73 metabolic variables.

TABLE 1 Background characteristics of study subjects

Characteristic	CHD ($N = 99$)	No CHD ($N = 197$)	p-Value
Age, years (median, IQR)	29 (26–33) ($N = 99$)	28 (26–33) ($N = 197$)	NS*
BMI (kg/m^2)			NS*
−18.49	2% ($N = 2$)	2% ($N = 4$)	
18.5–25	60.6% ($N = 60$)	59.4% ($N = 117$)	
25.01–30	23.2% ($N = 23$)	24.4% (N = 48)	
30.01–35	8.1% (N = 8)	8.1% ($N = 16$)	
35.01-	6.1% ($N = 6$)	6.1% ($N = 12$)	
Sex of the child			
Boy	74.7% ($N = 74$)	74.6% ($N = 147$)	NS**
Girl	25.3% ($N = 25$)	25.4% ($N = 50$)	
Parity			
Nulliparous	25.3% ($N = 25$)	33.5% (N = 66)	NS**
Multiparous	74.7% ($N = 74$)	66.5% (N = 131)	
Smoking during pregnancy			
Non-smoker	82.5% ($N = 80$)	85.9% ($N = 164$)	NS**
Smoker	17.5% ($N = 17$)	14.1% ($N = 27$)	
Oral glucose tolerance test done			
Yes	39.4% ($N = 39$)	43.1%($N = 85$)	NS**
Oral glucose tolerance test abnormal if done			
Yes	28.2% ($N = 11$)	24.7% ($N = 21$)	NS**
Number of fetuses			NS**
1	96% ($N = 95$)	98.5% ($N = 194$)	
2	4% ($N = 4$)	1.5% ($N = 3$)	
Method of childbirth			NS**
Spontaneous vaginal birth	74.7% ($N = 74$)	75.1% ($N = 148$)	
Ventouse cup	7.1% ($N = 7$)	7.1% ($N = 14$)	
Elective caesarean section	4% ($N = 4$)	6.6% ($N = 13$)	
Urgent caesarean section	13.1% ($N = 13$)	7.1% ($N = 14$)	
Emergency caesarean section	1% ($N = 1$)	2.5% ($N = 5$)	
Vaginal breech birth	0% ($N = 0$)	1.5% ($N = 3$)	
Gestational age, d (median, IQR)	278 (270–284) ($N = 99$)	281 (275–286) ($N = 197$)	0.01*
Birth weight, SD units (mean, SD)	−0.311 (1.16) ($N = 97$)	−0.060 (1.085) ($N = 197$)	NS***
Birth height, SD units (mean, SD)	−0.097 (1.027) ($N = 70$)	−0.059 (1.054) ($N = 197$)	NS***
Head circumference, SD units (mean, SD)	−0.603 (1.017) ($N = 62$)	0.074 (1.029) ($N = 196$)	<0.01***

Note: Values are means (standard deviation, *SD*) for normally distributed and medians (interquartile range, IQR) for skewed variables.
Abbreviations: BMI, body mass index; NS, nonsignificant.
*Mann–Whitney *U*-test.
**Chi-square test of independence.
***Independent samples *t*-test.

Conditional logistic regression was performed to assess the impact of higher metabolic measure concentration on the likelihood that a mother would have a child with TGA. This analysis took into account the stratification and matching of the data. The same statistical method was used in the analysis of the subgroups of BMI over 25 and 30. BMI was included as a covariate. Pooled estimate of odds ratio of the all metabolic variables were calculated by meta-analysis methods using fixed-effects model with inverse-variances weighting. Because of the

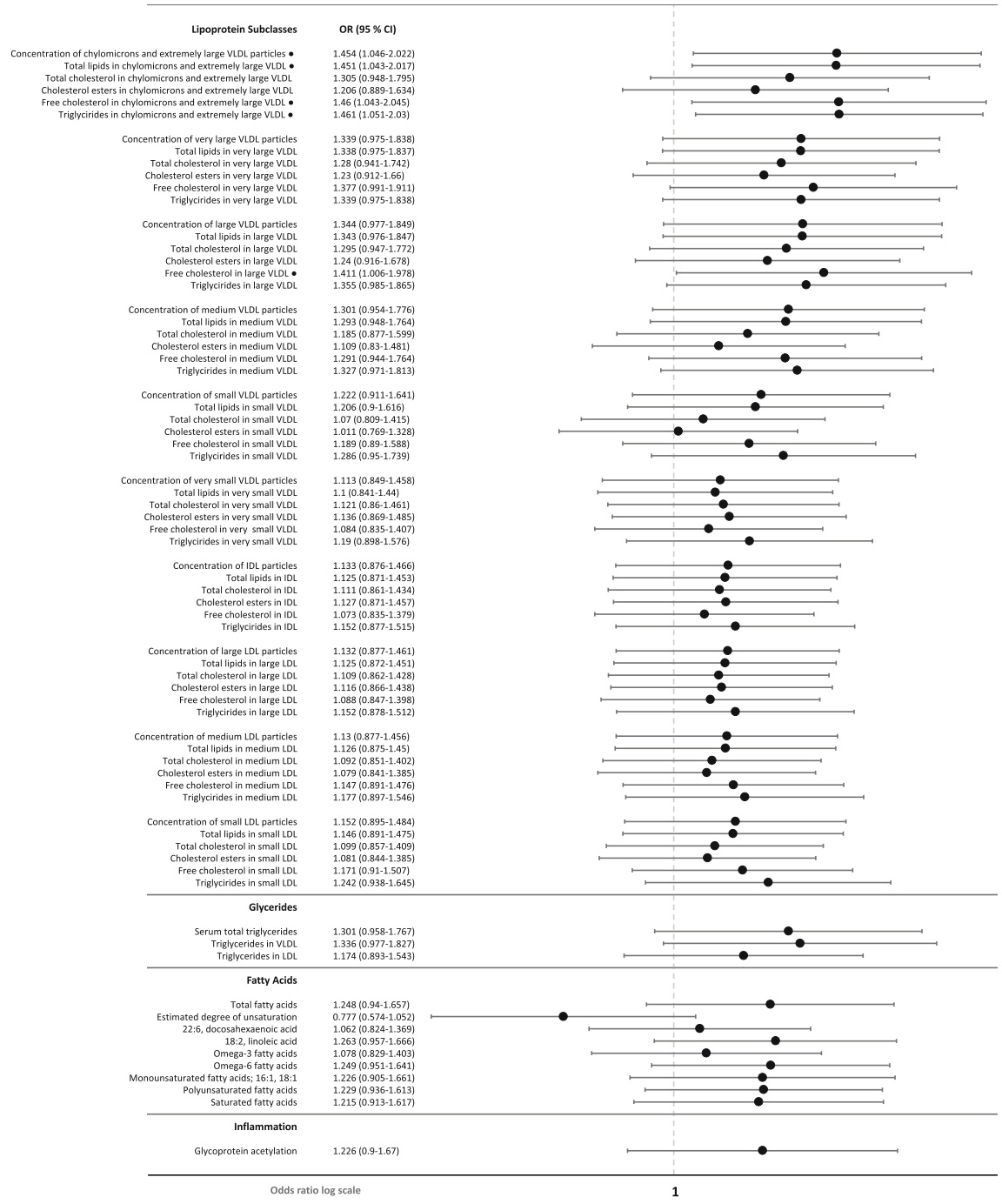

FIGURE 1 Univariate conditional logistic regression analysis of the metabolic measures in TGA versus control pregnancies. BMI was included as a covariate in the analysis. CI, confidence interval; OR, odds ratio

correlated nature of the data, principal component analysis was used to evaluate the appropriate number of independent tests for the correction of multiple testing (Kujala et al., 2013; Wang et al., 2016). In our analysis, principal component analysis revealed the presence of four components explaining 99.1% of the variation and therefore p-value < 0.0125 (0.05/4) was used as a threshold for statistical significance (data not shown).

All statistical analyses were conducted with SPSS versions 25 and 27 (IBM Corp.) except pooled odds ratios were calculated with MetaXL version 5.3 (EpiGear International Pty Ltd).

This study was conducted according to the guidelines set in the Declaration of Helsinki and the study protocol was reviewed and approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS).

Participants gave informed consent for their samples to be deposited in the Biobank for research purposes.

3 | RESULTS

The baseline characteristics of the study population are presented in Table 1. A total of 39 cases (39.4%) and 85 controls (43.1%) had undergone the 75 g oral glucose tolerance test (OGTT). Of these, the OGTT was abnormal in 11 (28.2%) of mothers with TGA children and in 21 (24.7%) of the controls (p-value 0.68). The distribution of maternal BMI was similar in the two groups, and 37.4% of cases and 38.6% of expectant mothers in the control group were overweight or obese (Table 1). The head circumference (HC) differed in the two groups as TGA infants had significantly lower HC in SD units adjusted for GA when compared to the controls (p-value <0.01, CI–0.971- [−0.382]) (Table 1).

The metabolic marker values are presented in Figure 1. Five of the metabolic measures (concentration of chylomicrons and extremely large VLDL particles, total lipids in chylomicrons and extremely large VLDL, free cholesterol in chylomicrons and extremely large VLDL, triglycerides in chylomicrons and extremely large VLDL, free cholesterol in large VLDL) were found to be higher in TGA pregnancies in the univariate analyses ($p < 0.05$). However, after multiple testing correction they did not remain statistically significant (p-value < 0.0125). There was no statistically significant difference in metabolic markers explaining the smaller HC in TGA neonates and there was no correlation between HC and metabolic markers measured (data not shown). In addition, no statistically significant differences after multiple testing correction were observed between those with and without an OGTT (data not shown).

Pooled odds ratio (OR) of the all metabolic variables in the original population was 1.18 (95% CI 1.14–1.22, $N = 296$, total). As a sensitivity analysis, we repeated the analyses in the subgroups of maternal BMI over 25 and 30 only. The pooled ORs of the all metabolic variables was slightly higher in the group with a BMI over 25 (OR = 1.25, 95% CI 1.19–1.32, $N = 111$, total) and significantly higher in the group with a BMI over 30 (OR = 1.95, 95% CI 1.76–2.16, $N = 42$, total) compared to the original population. BMI was included as a covariate in the analysis.

4 | DISCUSSION

This study of maternal first-trimester metabolomic markers suggests that maternal early pregnancy metabolic profile may be associated with a risk for TGA in the offspring, especially in overweight and obese mothers. This is an important finding when planning preventive measures, especially as the prevalence of obesity in women of childbearing age is increasing worldwide (Poston et al., 2016). In the United States, the prevalence of prepregnancy obesity increased by 8% from 2011 to 2015 (Deputy et al., 2018), and the increase continued from 26.1% in 2016 to 29% in 2019 (Driscoll & Gregory, 2020). In a Swedish population-based study with 1,022,330 women, the prevalence of prepregnancy obesity increased from 3.8% to 10.5% between 1983 and 2013 (Lundberg et al., 2021). We chose to study TGA, as maternal obesity has been associated with this CHD subgroup (Hautala et al., 2019; Persson et al., 2019), and the defect can be clearly defined anatomically. However, even with a national 10-year cohort the number of affected individuals is limited. Further studies, with larger study samples are needed especially in women with a BMI over 25 and 30 to demonstrate definite associations and potential dose response effects.

In the univariate analysis, slightly higher concentrations of four subtypes of extremely large VLDL particles and one subtype of large VLDL particles were observed in mothers with TGA in their offspring compared with mothers with a healthy child. Although not reaching statistical significance after multiple testing correction, the trend in our BMI-matched cohort could indicate that the maternal early-pregnancy lipid profile is associated with the likelihood of TGA development. At least two previous studies have indicated causal associations between maternal lipid profile and risk for CHD in the offspring. One recent study demonstrated that higher maternal TG, Apo-A1, and TC/HDL-C levels in early pregnancy associated with an increased risk for CHD in the offspring, including both mild and severe cases where ventricular septal defects formed the largest CHD group (Cao et al., 2021). Another study of the maternal lipid profile 16 months after the pregnancy showed higher total cholesterol, LDL, and apolipoprotein B among mothers with a child with CHD compared to controls. However, as the samples were collected after the pregnancy, definitive conclusions of the causal associations cannot be made. (Smedts et al., 2012) Nevertheless, the findings are interesting and point towards a potential role of maternal metabolomics beyond glucose in disease development.

The most important cardiac structures develop during early pregnancy. Higher early-pregnancy metabolic markers, such as increased concentrations of VLDL particles in several sizes and of small and medium sized HDL particles, have been demonstrated in women who develop GDM in later pregnancy compared to non-diabetic women (Mokkala et al., 2020). In obese mothers

with GDM, elevated lipids and lipoprotein constituents in VLDL subclasses, and greater triacylglycerol enrichment across lipoprotein particles, among other differences, were detected at least 10 weeks prior to the diagnosis of GDM (White et al., 2017). Moreover, a meta-analysis concluded that triglycerides are remarkably elevated in women with GDM across the entire pregnancy compared with women without increased insulin resistance (Ryckman et al., 2015). These previous findings emphasize the connection between an abnormal early-pregnancy metabolomic profile and the later development of GDM. Our finding that the subtypes of extremely large VLDL particles tended to be elevated in mothers of TGA infants points towards an abnormal lipid metabolism being a potential risk factor for the developing cardiac structures and could be a contributing factor in GDM associated risk for CHD in the offspring.

The molecular mechanisms behind maternal metabolic status and the development of CHD in the offspring remain largely unknown. Endothelial dysfunction and increased oxidative stress is one proposed mechanism. Excess abdominal adipose tissue both subcutaneously and viscerally is correlated with circulating inflammatory biomarkers and oxidative stress (Pou et al., 2007). Biomarkers of oxidative stress, such as concentrations of homocysteine and oxidized glutathione involved in the transsulfuration pathway, have been shown to be significantly higher in women with pregnancies affected by congenital heart defects than in women with normal pregnancies (Hobbs et al., 2005). In mice studies, endothelial dysfunction and endothelial nitric oxide synthase (eNOS) deficiency have been associated with increased risk for congenital septal defects and heart failure (Feng et al., 2002). ENOS is activated by insulin (Steinberg et al., 1994) and adiponectin (Chen et al., 2003) but in obesity and diabetes mellitus these protective mechanisms are decreased (Helle & Priest, 2020). Both maternal obesity (Jansson et al., 2008) and GDM (Worda et al., 2004) are associated with lower serum adiponectin levels during pregnancy. Moreover, improving eNOS coupling with oral supplementation of a cofactor for nitric oxide synthase in diabetic mothers has been shown to prevent the development of CHD in the offspring in mice studies (Engineer et al., 2018). Oxidative stress was not studied in our cohort but we investigated a circulatory inflammatory marker, GlycA, which is a novel measure of low-grade inflammation. In a recent study, GlycA was found to predict GDM during early pregnancy in overweight and obese women (Mokkala et al., 2020). In another study with a population of 26,539 women followed for 16 years, GlycA levels at the baseline correlated with the risk of diabetes (Akinkuolie et al., 2013) We found no statistically significant difference between cases and controls in the GlycA levels, but additional inflammation markers could be studied in this context.

The strengths of our study included the use of national registries that are mandatory and of high quality (Gissler et al., 1995; Haukka, 2004). The TGA diagnoses were verified from patient records. Since the diagnosis of CHD is made at the earliest during the late second trimester, third trimester, or postnatally, examining early pregnancy maternal biomarkers in CHD pregnancies poses a challenge. Although CHD is the most common congenital malformation, the incidence remains rather low, and tens or hundreds of thousands of samples are needed to achieve sufficient sample sizes for screening studies. Our approach, which used screening samples collected for other purposes, allowed us to retrospectively pick samples from the pregnancies of interest collected during several years. The samples were collected during the first trimester of pregnancy, representing the circumstances during cardiac morphogenesis (Dhanantwari et al., 2009; Sylva et al., 2014), making our approach relevant from a developmental view. A major weakness of our study was that due to sample handling procedures, we were unable to analyze the exact blood glucose levels and metabolic markers associated with it. However, the prevalence of diabetes was similar in both groups, as was the proportion of OGTTs performed, so it is likely that these would not act as confounding factors in the comparisons. Metabolic profile is affected by many factors in addition to BMI, such as physical activity and diet, which we did not have information on, and the possible confounding effect of these could not be adjusted for. Another weakness is the study sample size, which, although being a national cohort, is small. This diminishes the statistical power, especially in the subgroups of a BMI over 25 and 30. In addition, because of the sensitivity of the analysis process used on the metabolic samples, we were forced to exclude outliers potentially affected by the process. This type of congenital heart defect is found more frequently in Caucasians (Correa-Villaseñor et al., 1991), but future studies with samples from study subjects of different racial origins would be warranted. However, such a study might be challenged by the absence of similar national register data in other countries.

In conclusion, our study indicates a correlation between maternal first trimester metabolomics and the risk for TGA in the offspring, especially in overweight and obese mothers. Due to the small sample size, the role of individual biomarkers remains unclear, however, our results warrant further studies on this subject with larger patient cohorts. Identifying new risk biomarkers could potentially enable prevention with public health recommendations for women planning pregnancy and

help to direct resources into the screening of risk groups.

ACKNOWLEDGMENTS

This work was supported by the Finnish Foundation for Pediatric Research, the Academy of Finland, the University of Helsinki, the Finnish Medical Foundation, and the Pediatric Research Center of the Hospital District of Helsinki and Uusimaa (HUS). We are grateful for the statistical assistance of Tero Vahlberg.

DATA AVAILABILITY STATEMENT

The data used in this study has been obtained from the Finnish National Institute of Health and Welfare, and Biobank Borealis. This data has been used under license and is not publicly available to ensure privacy protection.

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How to cite this article: Huida, J., Ojala, T., Ilvesvuo, J., Surcel, H.-M., Priest, J. R., & Helle, E. (2023). Maternal first trimester metabolic profile in pregnancies with transposition of the great arteries. *Birth Defects Research*, *115*(5), 517–524. https://doi.org/10.1002/bdr2.2139