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Maternal mid-pregnancy glucose levels and risk of congenital heart disease in offspring

James R Priest, MD[1,2,3], **Wei Yang, MS**[3], **Gerald Reaven, MD**[3], **Joshua W. Knowles, MD PhD**[3], and **Gary M. Shaw, Dr PH**[3]

[1]Division of Pediatric Cardiology and Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, California USA

[2]Cardiovascular Institute, Stanford University School of Medicine, Stanford, California, USA

[3]Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA

[4]Division of Cardiovascular Medicine and Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, California, USA

Abstract

Importance—There is a well-described association between maternal diabetes and risk of congenital heart disease (CHD) in offspring. Though the clinical diagnoses of Type 2 diabetes or gestational diabetes are strong risk factors for CHD, sub-clinical abnormalities of glucose and insulin metabolism are common within the general population and could also confer risk for CHD.

Objective—We explored the potential association of two different CHD phenotypes in offspring with midpregnancy measures of glucose and insulin.

Design, Setting, and Participants—This is a case-control study from a cohort of 277 pregnant women in southern and central California carrying infants with tetralogy of Fallot (ToF) (n=55), d-transposition of the great arteries (dTGA) (n=42), or normal infants without CHD (n=180),

Exposures—Measurement of blood analytes related to maternal glucose metabolism taken from random non-fasting second trimester blood samples.

Main Outcome and Measures—We hypothesize that continuous measures of blood analytes related to maternal diabetes are related to odds of cardiac malformations. We measured serum insulin by a validated radioimmunoassay and glucose levels. Multivariable logistic regression models estimated the association between these levels and case status.

Results—Relative to maternal blood glucose levels of infants without cardiac malformations, we observed that maternal blood glucose levels in models including insulin were strongly associated with odds of ToF (adjusted Odds Ratio 7.54, 95%CI 2.30–24.69), but not with dTGA (adjusted OR 1.16, 95%CI 0.28–4.79).

Corresponding Author: James R Priest, Division of Pediatric Cardiology, Stanford University School of Medicine, 750 Welch Road Suite 300, Stanford, CA 94305, mobile (510) 213-2043, fax (650) 498-7452, jpriest@stanford.edu.

Conclusions & Relevance—These results represent a direct correlation of glucose as a continuous variable to odds of specific cardiac malformations. The association between serum glucose and odds of ToF indicates the need for additional epidemiological and mechanistic investigations into the risk conferred by insulin signaling and glucose metabolism during early pregnancy.

INTRODUCTION

Clinicians have long observed an association between maternal diabetes and risk of congenital heart disease (CHD) in offspring[1,23,4]. Retrospective cohort studies show that diabetic mothers with well-controlled blood glucose prior to pregnancy retain an elevated risk of offspring with CHD[5,6], suggesting an underlying maternal risk factor is correlated with both maternal diabetes and risk of CHD. The odds of the most common form of maternal diabetes, type 2 diabetes (T2D), is itself influenced by environmental risk factors (diet and physical activity) and inherited genetic risk factors for quantitative traits related to insulin sensitivity and processing, beta-cell function, and glucose metabolism[78]. Additionally, there is emerging experimental evidence of an age-related maternal risk factor for CHD which is modifiable by exercise[9], which could be consistent with many of the environmental, behavioral, or genetic risk factors for diabetes. The relationship between maternal T2D and CHD in offspring is poorly described, and the molecular mechanisms by which the clinical correlates of T2D (such as diet, exercise, glucose metabolism, and insulin sensitivity) may alter normal cardiac development are not known.

Though maternal diagnoses of T2D or gestational diabetes are strong risk factors for carrying a fetus affected with CHD, a binary diagnostic classification does not capture the wide spectrum of abnormal glucose metabolism within individuals who do not display overt disease [10]. Rather than using a binary diagnosis of diabetes, we explored the potential relationship of odds of CHD with measures of glucose metabolism. We assembled a cohort comparing midpregnancy measures of glucose and insulin in 97 mothers carrying fetuses with CHD to 180 women carrying normal fetuses without CHD or other malformations.

METHODS

Population Sample

The study population and collection methods have been previously described [11]; briefly sera were collected during the 15^{th}–18^{th} week of pregnancy from a multi-ethnic population based sample of women in southern and central California counties irrespective of fasting status or time of day. Samples were collected during the years of 2002–2007. Delivery outcome information and offspring phenotype was linked to serum specimens by the California Birth Defects Monitoring Program. The monitoring program abstracted case information from hospital reports and medical records. We excluded infants with documented chromosomal abnormalities or single gene disorders. We further selected infants with tetralogy of Fallot (ToF) (conotruncal category), d-transposition of the great arteries (dTGA) (non-conotruncal category). As described previously each case was ascertained by reviewing echocardiographic, catheterization, surgical, or autopsy reports. These samples included 111 mothers carrying a fetus with dTGA or ToF. We also randomly selected 223 age and

ethnicity matched women who contributed mid-pregnancy specimens that were collected during the same time period and delivered normal infants without CHD or other malformations (controls) as determined by the California Birth Defects Monitoring Program. All samples were obtained with approval from the California Health and Welfare Agency Committee for the Protection of Human Subjects.

Sample Collection & Storage

This study employed specimen data from the California Biobank (https://www.cdph.ca.gov/programs/GDSP/Pages/California%20Biobank%20Program.aspx) - a large and unique mid-pregnancy serum specimen bank of pregnancies in California. Serum specimens in this bank derive from approximately 70% of all California women and were obtained during the 15th–18th week of pregnancy. These sera specimens were collected from women who resided in selected regions of California (Orange, San Diego, and Central Valley counties) as part of the California prenatal screening program that offers three types of screening tests to pregnant women in order to identify individuals who are at increased risk for carrying a fetus with a specific birth defect. The collection and processing of specimens has the following steps: 1) samples were taken at draw stations using BD™ Vacutainer 3.5 mL serum separator tubes with no anticoagulants or preservatives and centrifuged within 30 minutes; 2) samples were received by designated clinical laboratories from draw stations at room temperature, on average 3.0 days after draw; 3) prenatal screening assays were run on samples usually on the day received; 4) samples were refrigerated up to 7 days if further testing was necessary; 5) samples were sent on cold packs via overnight mail to the California Biobank for storage bank; and 6) samples were aliquoted, labeled with barcodes, and frozen at −70°C within an average of 3.5 days of receipt at the California Biobank.

Insulin and Glucose Measurements

To measure two analytes, sera were diluted with phosphate buffered saline. Insulin was measured from sera by RIA using a kit for human insulin (Catalog # HI-14K) from Millipore (St. Charles, MO). Glucose was analyzed using the hexokinase method on the cobas c501 using kits from Roche Diagnostics (Indianapolis, IN) at the Diabetes Research Center (Washington University, St. Louis, MO, USA). Typical observed CV for the assays is <8.0% for Insulin RIA, and <1.2% for glucose. After testing 334 total samples (223 control, 64 ToF, 47 dTGA), we excluded from analysis 57 samples with glucose measurements < 63 mg/dL (43 control, 9 ToF, 5 dTGA), a value incompatible with normal cognition at the time of the blood draw which likely reflects a delay in sample processing[12]. Insulin values less than the limit of detection (6.4 uU/mL) were assigned a value of 6.4 uU/mL.

Statistical Methods

Glucose and insulin levels were compared between cases and controls using standard descriptive statistics. Both glucose and insulin were analyzed in log base 2 scale, which were normally distributed. Multivariable logistic regression models were used to estimate the association between glucose and insulin levels and the odds of ToF and dTGA; results are presented as adjusted odds ratios with 95% confidence intervals. We evaluated the potential for non-linear effects using non-linear terms and splines. We did not observe statistical evidence of non-linearity. Glucose homeostasis depends on secretion of insulin, therefore,

we constructed a logistic regression model that included both log glucose and log insulin values, along with an interaction term for their combination. No significant interaction between glucose and insulin was observed. All models adjusted for maternal age (years) and race/ethnicity (Hispanic; white, non-Hispanic), which were obtained from intake forms associated with the screening program. Additionally we conducted a sensitivity analysis with the identical analytical approach, excluding 5 subjects with a serum glucose greater than 200 mg/dL (no control subjects, 4 ToF, 1 dTGA), which is an accepted demarcation indicating T2D[13]. All analyses were performed using SAS 9.4.

RESULTS

We analyzed 42 samples from mothers carrying a fetus with dTGA, 55 maternal samples with a fetus with ToF, and 180 control samples (Table 1). Serum glucose values were elevated in the ToF maternal samples (median 97 mg/dL) relative to controls (median 91.5 mg/dL) ($p = 0.0112$, Wilcoxon rank sum test), a phenomenon not observed in the dTGA maternal samples relative to controls (Table 1). In logistic regression models using transformed glucose and insulin values adjusting for ethnicity and maternal age at sample collection, we observed that glucose values maintained a strong relationship with odds of ToF (odds ratio (OR) 4.54, 95%CI 1.71–12.05) that was not observed in the dTGA group (adjusted OR 0.69, 95%CI 0.19–2.44) (Table 2, Model 1).

Homeostatic regulation of serum glucose is dependent on insulin secretion and thus the two values are strongly interdependent. Therefore we constructed a logistic model including both log glucose and log insulin values. Accounting for insulin values in the adjusted model, log glucose values displayed an even stronger association with odds of ToF (adjusted OR 7.54, 95%CI 2.30–24.69) than in the univariable model not including insulin. This relationship was not observed between log glucose and dTGA (adjusted OR 1.16 95%CI 0.28–4.79) (Table 2, Model 2).

Examination of analyte values revealed that 5 individuals (4 from the ToF group, 1 from the dTGA group) showed random glucose values greater than 200 mg/dL, an accepted criterion for the clinical diagnosis of diabetes. To exclude the possibility that the observed association between glucose level and odds of ToF was driven by this small number of potentially overtly diabetic subjects, we performed a sensitivity analysis by removing individuals with serum glucose values greater than 200 mg/dL. Despite exclusion of these individuals, we still observed a robust association between log glucose and ToF (adjusted OR 4.61, 95%CI 1.14–18.67) that remained absent in the dTGA group (adjusted OR 0.68, 95%CI 0.15–3.12) (Table 3).

DISCUSSION

In this case-control study from a large California cohort we observed that a random maternal glucose measured during the second trimester was strongly associated with odds of delivering infants with ToF compared to women who delivered infants without structural malformations. This association persisted after controlling for age and ethnicity, adjusting for insulin measures, and even after excluding mothers with glucose values indicative of

overt diabetes. These data are consistent with the long recognized association between maternal diabetes and congenital heart disease [1,2], and suggest that there may be additional unmeasured risk within the general population that includes pre-diabetic individuals who do not carry a diagnosis of diabetes.

Blood glucose levels are influenced by a variety of factors such as diet, exercise, beta cell function, and insulin resistance, thus glucose levels may simply be a marker of risk conferred by another physiological process. Though we directly measured insulin levels in these women, insulin resistance cannot be directly assessed without a fasting sample or glucose tolerance protocol. The question therefore remains if elevated blood glucose or a variety of correlated but independent traits such as beta cell function, exercise or insulin resistance is behind the observed association.

It is important to note that cardiac development is largely complete by the second trimester when these blood samples were drawn[14]. There are reasonable clinical data suggesting that second trimester glucose metabolism is well correlated with maternal physiology in both first trimester and the pre-conception period[15–17]. However measurements of glucose, insulin, insulin resistance and clinical correlates from the time period encompassing pre-conception and the first trimester in mothers carrying infants affected with CHD are necessary to confirm the observed associations. Though it would be inconsistent with the current understanding of maternal-fetal glucose homeostasis, we cannot exclude the possibility that carrying a fetus with ToF impacts maternal glucose metabolism[18,19].

The effect of maternal serum insulin on risk for CHD has not been previously assessed, except indirectly in population based studies including women treated with insulin[6]. Even diabetic mothers treated with insulin with well-controlled glucose levels retain an increased risk of CHD in offspring, which could be related either an underlying insulin resistance or conceivably by treatment related hyperinsulinemia. Non-diabetic mothers with insulin resistance and compensatory hyperinsulinemia may represent a parallel situation. Though exogenously administered insulin falls in FDA Pregnancy Category B[20,21], insulin interacts with the IGF-1 pathway and may impact fetal growth and development when crossing the placenta[22,23]. Additionally, insulin signaling in other tissues is involved in a variety of human diseases[24] However in our study, random insulin levels during pregnancy were not directly associated with risk of CHD. Though risk of CHD has not been conclusively related to the ethnicities included in the study population, there are well described ethnic differences in glucose metabolism within women of childbearing age accounted for in the adjusted model[25,26].

In conclusion, we observed an association of maternal glucose levels with the risk of ToF in offspring. If confirmed in larger studies conducted earlier in pregnancy, these observations could have important public health implications for identifying women at odds of carrying infants with CHD and targeting interventions to improve glucose homeostasis (such as exercise, maintaining a healthy weight). Additional epidemiological and experimental work is necessary to describe the causal risk factor related to both serum glucose levels and cardiac development, and to understand the mechanism by which risk is conferred from mother to child.

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AT A GLANCE

- There is a well-described association between maternal diabetes and risk of congenital heart disease (CHD) in offspring, but whether the risk extends to non-diabetic individuals with abnormal glucose homeostasis is not known.
- In a cohort of 277 women carrying infants with or without CHD we observed a strong association with maternal glucose levels that was specific to tetralogy of Fallot (adjusted odds ratio 7.54, 95%CI 2.30–24.69).
- These results indicate a direct correlation of glucose as a continuous variable in non-diabetic individuals to odds of a specific cardiac malformation.
- Additional investigation into blood glucose levels and related but independent physiological traits (such as beta cell function, exercise and insulin resistance) are needed earlier in pregnancy to confirm these findings.

Table 1

Characteristics of mothers carrying fetuses with congenital heart defects and normal controls, California 2002 through 2007

	Controls (n=180)		**ToF (n=55)**		**dTGA (n=42)**	
Age (years) [2]	No.	%	No.	%	No.	%
<25	76	42.2	16	29.1	12	28.6
25–29	45	25.0	16	29.1	13	31.0
30–34	41	22.8	12	21.8	15	35.7
≥35	18	10.0	11	20.0	2	4.8
Race/Ethnicity	No.	%	No.	%	No.	%
Hispanic	131	72.8	33	60.0	25	59.5
White non-Hispanic	49	27.2	22	40.0	17	40.5
	Median	IQR	Median	IQR	Median	IQR
Glucose (mg/dL)	91.5	19.0	97.0	23.0	90.0	23.0
			p = 0.0112 [3]		*p = 0.1812* [3]	
	Median	IQR	Median	IQR	Median	IQR
Insulin (uU/mL)	18.8	26.8	14.3	29.6	13.1	21.0
			p = 0.3461 [3]		***p = 0.0479*** [3]	

[1] Percentages may not equal 100 owing to missing data or rounding.

[2] Maternal age at sample collection

[3] Wilcoxon rank sum test for category (ToF or dTGA) compared to non-malformed controls

IQR: Inter-quartile range

Table 2

Logistic regression models of maternal insulin and glucose levels in subcategories of congenital heart disease for all subjects

ToF vs. Controls				
	Model 1 [1]		**Model 2** [2]	
Analyte	**Crude OR (95%CI)**	**Adjusted OR (95%CI)** [2]	**Crude OR (95%CI)**	**Adjusted OR (95%CI)** [2]
Log_2(glucose)	**4.83 (1.89, 12.40)**	**4.54 (1.71, 12.05)**	**8.60 (2.72, 27.24)**	**7.54 (2.30, 24.69)**
Log_2(Insulin)	0.95 (0.75, 1.19)	0.97 (0.76, 1.23)	**0.74 (0.57, 0.98)**	0.78 (0.59, 1.02)

dTGA vs. Controls				
	Model 1		**Model 2**	
Analyte	**Crude OR (95%CI)**	**Adjusted OR (95%CI)**[1]	**Crude OR (95%CI)**	**Adjusted OR (95%CI)**[1]
Log_2(glucose)	0.68 (0.19, 2.38)	0.69 (0.19, 2.44)	1.24 (0.30, 5.07)	1.16 (0.28, 4.79)
Log_2(Insulin)	0.76 (0.57, 1.02)	0.78 (0.58, 1.04)	0.75 (0.54, 1.03)	0.77 (0.56, 1.06)

[1] Model 1 shows results for glucose or insulin alone. Model 2 shows results with both analytes simultaneously evaluated

[2] Adjusting for maternal race/ethnicity (Hispanic, and White non-Hispanic) and maternal age at sample collection (continuous, in years).

Table 3

Sensitivity analysis; logistic regression of maternal insulin and glucose levels in subcategories of congenital heart disease for subjects with random glucose less than 200 mg/dL

ToF vs. Controls				
	Model 1 [1]		**Model 2** [1]	
Analyte	**Crude OR (95%CI)**	**Adjusted OR (95%CI)** [2]	**Crude OR (95%CI)**	**Adjusted OR (95%CI)** [2]
Log_2(glucose)	2.93 (0.96, 8.96)	2.76 (0.87, 8.74)	**5.45 (1.41, 21.08)**	**4.61 (1.14, 18.67)**
Log_2(Insulin)	0.93 (0.73, 1.18)	0.95 (0.75, 1.22)	0.78 (0.59, 1.03)	0.82 (0.61, 1.09)

dTGA vs. Controls				
	Model 1		**Model 2**	
Analyte	**Crude OR (95%CI)**	**Adjusted OR (95%CI)**[1]	**Crude OR (95%CI)**	**Adjusted OR (95%CI)**[1]
Log_2(glucose)	0.41 (0.10, 1.60)	0.41 (0.10, 1.66)	0.72 (0.16, 3.33)	0.68 (0.15, 3.12)
Log_2(Insulin)	0.74 (0.55, 0.99)	0.75 (0.56, 1.01)	0.76 (0.55, 1.05)	0.78 (0.56, 1.08)

[1] Model 1 shows results for glucose or insulin alone. Model 2 shows results with both analytes simultaneously evaluated

[2] For all subjects, adjusting for maternal race/ethnicity (Hispanic, and White non-Hispanic) and maternal age at sample collection (continuous, in years).