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First Trimester Plasma Glucose Values in Non-Diabetic Women are Associated with Risk for Congenital Heart Disease in Offspring

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In a retrospective study of 19,171 mother-child dyads, elevated random plasma glucose values during early pregnancy were directly correlated with increased risk for CHD in offspring. Plasma glucose levels proximal to the period of cardiac development may represent a modifiable risk factor for CHD in expectant mothers without diabetes.

Maternal diabetes has long been recognized to be a risk factor for congenital heart disease (CHD) in offspring[1,2]. Despite the different pathophysiological mechanisms, both type 1 and type 2 diabetes contribute to the risk of CHD[3], and although attenuated in women with improved glucose control, the risk of CHD does not revert to baseline [4,5]. Population studies suggest the presence of acute diabetic complications during pregnancy significantly increase risk of all types of CHD in offspring[1]. Interestingly, a recent case-control study in non-diabetic mothers displayed elevated random plasma glucose values during the second trimester in mothers of offspring with tetralogy of Fallot compared with mothers whose offspring did not have CHD[6]. These findings suggest that risk of CHD in the fetus conferred by maternal diabetes may be related to greater variations in plasma glucose levels in diabetic

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mothers rather than, to long-term glucose values (HbA1c), plasma insulin level or a clinical diagnosis of diabetes. In addition, it raises the question of whether transient plasma glucose elevations even in non-diabetic mothers could predispose offspring for CHD.

Though studies of glucose metabolism performed during the second trimester appear to be strongly linked to glucose metabolism during both the peri-conceptional period and first trimester[7–9] cardiac morphogenesis occurs during the first trimester between gestational weeks 4–10[10]. Most clinical measurements of glucose metabolism such as the oral glucose tolerance test (OGTT) are typically performed during the second trimester after the heart has already formed. Therefore we sought to determine if random non-fasting plasma glucose levels measured proximally to the period of cardiac development encompassing the first trimester were related to the risk of CHD both in diabetic and non-diabetic mothers.

Methods

We assembled a retrospective multi-institutional cohort of 19,107 mother-child dyads of mothers aged 16 or older for which prenatal information and postnatal diagnoses were available (Stanford Healthcare years 2009–2014 (n = 9,742), and Geisinger Health System years 2010–2015 (n = 9,365). We excluded offspring with a diagnosis of aneuploidy or 22q11.2 deletion syndrome, multiple pregnancies, and women with extreme body mass index (BMI) measures (<15 or >50). Estimated dates of conception were interpolated in a hierarchical fashion from 280 days prior to birth, unless more specific data was available from icd9 codes (765.11–765.19) for prematurity status. Given some ambiguity in estimation of exact timing of laboratory measurements during pregnancy, we obtained all random plasma glucose measurements performed between four weeks prior to the estimated date of conception until the end of the 14th gestational week, and also results of the 1-hour oral glucose tolerance test (OGTT) typically completed during late second trimester. If multiple measurements were available, we selected the single highest value for analysis as delayed separation of the plasma can decrease the glucose value of the sample. We included plasma glucose measurements in our analysis, and specifically excluded glucose measurements designated as “fasting” or from glucose tolerance tests within the electronic medical record. Because insulin values are rarely measured as a component of routine clinical care, we did not incorporate insulin or other measures of insulin resistance within our analysis other than OGTT. A diagnosis of CHD was defined by the presence of any type of CHD (ICD9-codes 745.5–747.49) in the offspring. For individuals with OGTT and glucose measures, we performed logistic regression, and adjusted the model for known maternal risk factors for offspring with CHD, including presence of pregestational diabetes (defined by the presence of ICD9 codes 250–250.93), pre-pregnancy BMI, and maternal age at delivery. In a sensitivity analysis, we excluded mothers with pregestational diabetes. Power calculations were performed assuming an average glucose value of 89.3 mg/dL with a standard deviation of 6.2 mg/dL, demonstrating that in a group of 200 cases, 2000 controls displayed 80% power to detect an effect of 0.18 standard deviations between the 2 groups. Regression models were constructed using the R language for statistical computing.

Results

Review of electronic medical records at both study institutions identified 811 CHD-affected pregnancies and 18,296 without CHD. At the Stanford site where detailed diagnostic information was available for review, all categories of CHD were represented with half of cases (49.9%, n = 223) constituting isolated ventricular or atrial septal defects. Relative to the Geisinger cohort, which is a community based health system, the mothers at the Stanford cohort were older, with higher BMI, and a greater burden of pre-pregnancy diabetes (Table I). Plasma glucose values were measured at least once in 11.9%, and OGTT in 49.7% of mothers. Mothers with measured plasma glucose values were younger than mothers without measurements (median 26 vs 28 years), and the same applied for OGTT values (median 26 vs 30 years).

Among the women with relevant clinical measurements, higher plasma glucose (OR 1.08 per 10 mg/dL increase in glucose, 95% CI:1.03–1.12, $P < .001$) and higher 1-hour OGTT values (OR 1.06, 95% CI:1.02–1.10, p = 0.002) were both associated with increased risk for CHD offspring in unadjusted logistic models. After adjustment for clinical correlates of glucose metabolism including maternal age, pre-pregnancy BMI, and the presence of preexisting maternal diabetes (Table 2), higher random first trimester plasma glucose values remained associated with increased risk for CHD (adjusted OR 1.08 per 10 mg/dL increase in glucose, 95% CI:1.02–1.13, p = 0.003) and the association with 1-hour OGTT values was elevated but not statistically significant (adjusted OR 1.03, 95% CI:0.98–1.07, p = 0.214). In a sensitivity analysis excluding women with a preexisting diagnosis of diabetes (n=74), the positive association between a random plasma glucose value with risk for CHD among offspring was essentially unchanged (adjusted OR 1.09, 95% CI:1.02–1.14, p = 0.003) (Table 2).

Discussion

Our observations demonstrate that higher random plasma glucose values measured during early pregnancy correlate with increased risk for CHD in offspring of mothers who do not have diabetes. Furthermore, plasma glucose measured during early pregnancy was more associated with risk for CHD in offspring, compared with the OGTT which is often used to risk-stratify pregnancies for fetal-echocardiographic screening.

Previous clinical observations detect increased risk for CHD in offspring even in diabetic mothers with well controlled glucose levels[4,5], suggesting that the risk to offspring may be related to the variation in the plasma glucose levels. Although a lower HbA1c value reflects lower average glucose levels in the long term, fluctuation in glucose levels are likely higher in diabetic than in non-diabetic mothers. Transient high glucose is known to cause persistent epigenetic changes and altered gene expression in vascular cells during subsequent normoglycemia[11]. As cardiac development occurs early in pregnancy, and many important complex structures are formed during a short period of time, it is possible that even short elevations in glucose levels during critical time points can be enough to disturb cardiac development.

The exact mechanisms by which high glucose may impact cardiac development are not yet clear. Maternal diabetes has been most strongly associated with conotruncal defects, such as tetralogy of Fallot[3]. High glucose and augmented oxidative stress have been observed to inhibit migration of neural crest derived cells from the neural tube in study animals, leading to congenital heart disease[13,14]. Thus, if the results from animal studies can be generalized to humans, transient elevations in glucose values during critical periods of cardiac development might potentially disturb the CNC migration even in embryos of non-diabetic mothers and contribute to the risk of CHD in the fetus.

Pre-diabetes is observed in as many as 28% of women of childbearing age [15]. Given that increased risk for CHD continues to be measurable in women without a pre-existing diagnosis of diabetes both previously and now more fully in the data reported here, the contribution of maternal pre-diabetes to risk of CHD in offspring requires careful assessment in large prospective cohort studies. As plasma glucose levels are correlated with modifiable behaviors such weight, physical activity, and dietary habits, confirming these results in larger studies could provide additional data for pre- and early pregnancy health recommendations as a strategy to optimize the outcomes of pregnancy.

As a retrospective study, these findings are limited by bias inherent in selection of patients with glucose measurements and the ascertainment challenges inherent to working with data obtained from electronic medical records that did not include information on known risk factors for CHD such as maternal smoking, alcohol consumption, or infection. Early pregnancy plasma glucose measurements were present for only 13% of the mother-infant dyads, and the clinical reasoning for obtaining the glucose value was unknown, thus some values may be fasting or from other controlled states. The Geisinger cohort had individuals with multiple glucose measurements, which may be related to a bias toward more readily availability measurements from an integrated inpatient-outpatient electronic medical record. Indeed, the cohorts displayed differences attributable to the different roles that the 2 institutions play within their respective healthcare markets. The older maternal age, higher BMI, higher rates of pre-existing diabetes and CHD are illustrative of a “higher-risk” maternal cohort, which reflects the role of Stanford Healthcare as a regional and statewide quaternary referral center. In contrast, the Geisinger cohort may represent a less selective population with an “average risk” for adverse outcomes. However, glucose values were measured in similar frequencies in pregnancies with or without CHD (12.3 % of dyads with CHD, 13.6 % of dyads without CHD), which does not suggest selection bias related to clinical suspicion of CHD or any known correlates. The overall size of the cohort was not adequately powered to characterize the risk for specific CHD malformations. As such, larger prospective studies are necessary to confirm the generalizability of these findings.

A random plasma glucose value performed early in pregnancy may be a marker for risk of CHD in offspring in non-diabetic mothers. Though strongly influenced by common genetic loci, plasma glucose levels are correlated with modifiable behaviors such weight, physical activity, and dietary habits. If confirmed in large population based studies, plasma glucose values may represent a modifiable risk factor for CHD in expectant mothers and women planning pregnancy and a biomarker applicable to risk-stratification of pregnant mothers for prenatal echocardiography screening for CHD in the fetus.

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Abbreviations

CHD	congenital heart disease
OGTT	oral glucose tolerance test
BMI	Body Mass Index
ICD9	International Classification of Diseases, 9th Revision
CNC	Cardiac neural crest

References

1. The Infants Of Diabetic Mothers. BMJ. 1940; 1:1064.
2. Rowland TW, Hubbell JP, Nadas AS. Congenital heart disease in infants of diabetic mothers. J Pediatr. 1973
3. Øyen N, Diaz LJ, Leirgul E, Boyd HA, Priest J, Mathiesen ER, et al. Prepregnancy Diabetes and Offspring Risk of Congenital Heart Disease: A Nationwide Cohort Study. Circulation. 2016; 133:2243–53. [PubMed: 27166384]
4. Lisowski LA, Verheijen PM, Copel JA, Kleinman CS, Wassink S, Visser GH, Meijboom EH. Congenital Heart Disease in Pregnancies Complicated by Maternal Diabetes Mellitus. Herz. 2010; 35:19–26. [PubMed: 20140785]
5. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ. 2004 Apr 17.328:915. [PubMed: 15066886]
6. Priest JR, Yang W, Reaven G, Knowles JW, Shaw GM. Maternal mid-pregnancy glucose levels and risk of congenital heart disease in offspring. JAMA Pediatr. 2015; 169:1112–1116. [PubMed: 26457543]
7. Riskin-Mashiah S, Damti A, Younes G, Auslander R. Normal fasting plasma glucose levels during pregnancy: a hospital-based study. J Perinat Med. 2011; 39:209–211. [PubMed: 21241203]
8. Grewal E, Kansara S, Kachhawa G, Ammini AC, Kriplani A, Aggarwal N, et al. Prediction of gestational diabetes mellitus at 24 to 28 weeks of gestation by using first-trimester insulin sensitivity indices in Asian Indian subjects. Metabolism. 2012; 61:715–720. [PubMed: 22146095]
9. Endo S, Maeda K, Suto M, Kaji T, Morine M, Knoshita T, et al. Differences in insulin sensitivity in pregnant women with overweight and gestational diabetes mellitus. Gynecol Endocrinol. 2006; 22:343–349. [PubMed: 16785160]
10. Dhanantwari P, Lee E, Krishnan A, Samtani R, Yamada S, Anderson S, et al. Human Cardiac Development in the First Trimester: A High-Resolution Magnetic Resonance Imaging and Episcopic Fluorescence Image Capture Atlas. Circulation. 2009; 120:343–351. [PubMed: 19635979]
11. El-Osta A, Brasacchio D, Yao D, Pocai A, Jones PL, Roeder RG, et al. Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. J Exp Med. 2008 Sep 29.205:2409–17. [PubMed: 18809715]
12. Kirby ML, Turnage KL 3rd, Hays BM. Characterization of conotruncal malformations following ablation of “cardiac” neural crest. Anat Rec. 1985 Sep.213:87–93. [PubMed: 4073565]

13. Wu Y, Reece EA, Zhong J, Dong D, Shen WB, Harman CR, Yang P. Type 2 diabetes mellitus induces congenital heart defects in murine embryos by increasing oxidative stress, endoplasmic reticulum stress, and apoptosis. Am J Obstet Gynecol. 2016 Sep.215:366.e1–366.e10. [PubMed: 27038779]
14. Suzuki N, Svensson K, Eriksson UJ. High glucose concentration inhibits migration of rat cranial neural crest cells in vitro. Diabetologia. 1996 Apr.39:401–11. [PubMed: 8777989]
15. Herman W, Rothberg AE. Prevalence of Diabetes in the United StatesA Glimmer of Hope? JAMA. 2015; 314:1005–1007. [PubMed: 26348749]

Table 1

Measured parameters by enrollment site

	Stanford n = 9,742	**Geisinger n = 9,365**
Age in Years, median	31	25
Congenital Heart Disease, n (% of total)	447 (4.6%)	364 (3.9%)
Pre-pregnancy Diabetes, n (% of total)	60 (0.6%)	14 (0.1%)
Pre-pregnancy BMI, median (n, % total with measurements)	28.1 (9643, 99.0%)	25.1 (6112, 65.2%)
Early Plasma Glucose mg/dl, median (n, % total with measurements)	92 (903, 9.2%)	89 (1389, 14.8%)
OGTT 1 hour value mg/dl, median (n, % total with measurements)	122 (1825, 18.7%)	112 (7686, 82.1%)
More than one glucose measurement (n, % of those with glucose measurements)	5 (0.6 %)	386 (27.8%)
More than one OGTT measurement (n, % of those with glucose measurements)	306 (16.7%)	100 (1.3%)

Table 2

Logistic regression models for a) glucose and b)1 hour OGTT and risk for congenital heart disease in the offspring including and excluding mothers with diabetes. Model simultaneously included OGTT, maternal pre-pregnancy BMI, maternal age, and maternal diagnosis for diabetes mellitus (where applicable).

a) Models for Glucose				
	Including All Mother-infant Dyads (n=2233)		**Excluding Mother-Infant Dyads with Pre-Existing Maternal DM (n=2204)**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Glucose (mg/dL / 10)	1.079 (1.023–1.131)	0.003	1.086 (1.023–1.143)	0.003
BMI	1.007 (0.976–1.037)	0.656	1.004 (0.974–1.035)	0.775
Maternal Age	1.005 (0.972–1.038)	0.77	1.007 (0.974–1.040)	0.685
Maternal DM	0.687 (0.085–3.124)	0.674	n/a	n/a
b) Models for OGTT				
	Including All Mother-Infant Dyads (n=7147)		**Excluding Mother-Infant Dyads with Pre-Existing Maternal DM (n=7142)**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
OGTT 1 hour (mg/dL)	1.003 (0.998–1.007)	0.214	1.003 (0.998–1.007)	0.214
BMI	1.006 (0.986–1.025)	0.572	1.006 (0.986–1.025)	0.572
Maternal Age	1.029 (1.009–1.050)	0.004	1.029 (1.009–1.050)	0.004
Maternal DM	0.000 (NA-29.120)	0.976	n/a	n/a