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Fasting glucose concentrations and associations with reproductive history over 40 years of follow-up

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Abstract

Gestational diabetes mellitus (GDM) is the onset or first recognition of diabetes that occurs during pregnancy. We aimed to assess for trends in fasting blood glucose levels across the life-course among a cohort of women by reproductive history: nulligravid women, gravid women with and without a history of GDM. Women who had participated in the Bogalusa Heart Study as children were interviewed about their reproductive history, including GDM (n=358). We compared fasting blood glucose (mg/dL) measured after last pregnancy (or after age 40 among nulligravid women) across reproductive history groups in linear models adjusted for pre-pregnancy fasting blood glucose, body mass index, race, parity, and age at outcome measure. We fit a log-poisson model to estimate the associations with prediabetes risk after age 40. After adjustments, mean fasting glucose after age 40 was not different between gravid women without GDM history and nulligravid women. However, women with a history of GDM had mean fasting glucose 27 mg/dL greater than nulligravid women (95% CI=12.35, 41.64). Heterogeneity by race indicated Black women with a history of GDM had disproportionately elevated mean fasting glucose after age 40. Fasting blood glucose trends over the life-course differ among women by reproductive history, and race.

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Keywords

Pregnancy; insulin resistance; diabetes

Introduction

Gestational diabetes mellitus (GDM) is a condition defined as the onset or first recognition of diabetes – carbohydrate intolerance leading to hyperglycemia – during pregnancy. An estimated 4.6–9.2% of pregnant women in the US are diagnosed with GDM,[1] with markedly increased prevalence in recent decades.[2] Women with GDM are at increased risk for pregnancy and delivery complications including preeclampsia, gestational hypertension, and cesarean section.[3, 4]

Guided by life-course epidemiology theory – which posits that later-life health status is shaped by exposures occurring across an individual's life[5] – researchers have begun to piece together pathways of influence from preconception health to pregnancy health outcomes, and pregnancy health outcomes to later-life health. Women entering pregnancy with a history of chronic disease – including chronic hypertension - [6, 7, 8] stress,[9] or high body mass index[10, 11] are more likely to experience pregnancy complications including GDM. Women diagnosed with GDM, in turn, are 5–7 times more likely to develop type 2 diabetes mellitus (T2DM) within 5 to 10 years after pregnancy compared to women without a history of GDM.[12]

The physiologic demands of pregnancy act as stress-test, revealing underlying predispositions for vascular and endothelial dysfunction or unmasking sub-clinical disease. [13] Previous studies report that GDM in particular is an independent risk factor for long-term atherosclerotic and cardiovascular morbidities.[14, 15] While pregnancy health is an increasingly recognized sentinel of later-life chronic disease risk, previous literature is limited by a lack of information about pre-pregnancy health, and whether women who develop GDM and later life T2DM risk were at elevated risk even before they became pregnant. Some recent evidence supports plausible common mechanisms underpinning both infertility and T2DM risk, such that women with a history of infertility experience 20% greater risk of developing diabetes.[16]

The purpose of this study was to describe trends in fasting blood glucose levels among a cohort of women with varied reproductive histories and more than 40 years of follow-up. We compared fasting glucose levels across the life-course among women who never had a pregnancy, women who had at least 1 pregnancy but no history of GDM, and those with a history of GDM.

Materials and Methods

The Bogalusa Heart Study is a longitudinal study of cardiovascular health.[17] The study began enrolling school children in Bogalusa, Louisiana in 1973 and approximately every 2 years thereafter. Repeated exams continued through 1994, enrolling new children and following-up those previously enrolled. Exams included interviews, venipuncture after a 12-

hour fast, right-arm blood pressure measures in triplicate, and replicate anthropometric measures. Fasting plasma glucose level was obtained as part of a multiple chemistry profile (SMA20) with the multichannel Olympus Au-5000 analyzer (Olympus, Lake Success, NY).

Beginning in 2013, a follow-up study sought to re-contact and enroll women who had completed a Bogalusa Heart Study examination in childhood. Potential participants were contacted via phone call, mailing, or in person at the Bogalusa Heart Study field clinic. After consenting, subjects reported on their reproductive history, including ever having been given a diagnosis of gestational diabetes. Consenting participants signed release forms for prenatal, labor and delivery records for each pregnancy.

Women included in this analysis were those who had completed a fasting glucose blood draw during least one Bogalusa Heart Study exam prior to her first pregnancy (or prior to age 17 among women who were never pregnant) as well as at least one exam after age 40 (or after last pregnancy if older than age 40). The final sample included 358 women (Figure 1). We classified women into three groups for comparisons: nulligravid women, those who were pregnant at least once but never had GDM, and those who were pregnant at least once with a history of GDM. The Institutional Review Board at Tulane University approved this study.

Outcome

The primary outcome of interest was fasting blood glucose (mg/dL) measured after age 40. Five women reported pregnancies after age 40. For these women, all but 1 had additional fasting glucose measures taken at exams later than their age at final pregnancy and therefore only her post-pregnancy measures were retained. For women with multiple fasting glucose measurements occurring after 40 or last pregnancy, mean levels across exams served as the outcome in adjusted models. As a secondary outcome, we categorized fasting glucose measures as above or below the pre-diabetes threshold of ≥ 100 mg/dL.

Exposure and covariates

The primary exposure of interest was the three-category pregnancy history variable (nulligravid, gravid without any incidences of GDM, and gravid with at least one GDM pregnancy). Confounders included body mass index (BMI) at time of outcome measure (kg/m^2), parity (continuous), race (non-Hispanic [NH] black, NH white), and fasting blood glucose (mg/dL) measured at exams prior to the first pregnancy. The mean age across pre-pregnancy fasting glucose measures was 16.7 years. Therefore, we estimated the mean fasting glucose level at all exams prior to age 17 for nulligravid women to control for a similar “baseline” fasting glucose measure.

Statistical Analysis

Descriptive statistics characterized the analytic sample and compared covariate distributions across pregnancy history categories using chi-square and ANOVA tests. We fit crude and adjusted linear regression models to compare mean fasting glucose at age 40 by reproductive history. Given the significant race-associated difference in incidence of T2DM, we tested for multiplicative interaction by race. Finally, we fit log-Poisson models to estimate the relative

risk (and 95% confidence intervals) for having prediabetes at age 40 or later across the three groups of women.

Results

Of the 358 women included in this analysis, 41 women experienced GDM during at least one pregnancy (Table 1). Most (78%) had been pregnant at least once and never had GDM. Mean age at first pregnancy among the gravid women was 22.2 (standard deviation=5.1). Ten percent of women in the sample (n=37) had never been pregnant. All women self-identified as either NH black (32%) or NH white (68%). Most (46%) had a BMI at age 40 or later in the obese range (>30 kg/m²) while 26% were under or normal weight (<25 kg/m²) and 28% were overweight (25–29.9 kg/m²).

No women had mean baseline glucose measures falling above the diabetes threshold of 126 mg/dL, and none reported a history of diabetes. Crude mean baseline fasting glucose did not differ between women who would go on to become pregnant but never have GDM (mean=83.9 mg/dL) and those who would develop GDM (mean=84.6 mg/dL), but was significantly higher among nulligravid women (mean=88.7 mg/dL, $p<0.01$; Table 1). Crude mean fasting glucose levels at age 40 or later did not differ between nulligravid women (mean=89.5 mg/dL) and gravid women without a history of GDM (mean=91.3 mg/dL), but were significantly higher among gravid women with GDM (mean=114.2 mg/dL, $p<0.01$). There were 42 women (11.7%) whose fasting glucose at age 40 or later measured in the prediabetes range (≥ 100 mg/dL but <126 mg/dL), and 21 (5.9%) with measures ≥ 126 mg/dL. Almost 40% of the women who experienced GDM had fasting glucose levels in the prediabetes range or higher after age 40 or their last pregnancy.

These patterns of associations were consistent in adjusted models (Table 2). After adjustments, women with a history of GDM had mean fasting glucose 27 mg/dL greater than women who were never pregnant (95% CI=12.35, 41.64). Further, the test for interaction by race indicated heterogeneity in the effect of pregnancy history on post-pregnancy or after age 40 glucose levels (Table 2). Among black women with a history of GDM, mean fasting glucose after age 40 was 64.5 mg/dL greater than nulligravid black women (95% CI=21.32, 107.62), compared to a difference of only 17.5 mg/dL between NH white women with GDM and nulligravid white women (95% CI=5.65, 29.44), although confidence intervals overlapped.

Finally, log-Poisson models confirmed an elevated risk of prediabetes after age 40 among women with a history of GDM. Compared to nulligravid women, their risk of prediabetes after age 40 and last pregnancy was nearly 4 times higher (RR=3.70, 95% CI=1.13, 12.04). There was no difference in risk of prediabetes between parous women without GDM and nulligravid women (RR=1.43, 95% CI=0.49, 4.20). Elevated baseline fasting glucose was associated with an increased risk of prediabetes by 5% for every 1 mg/dL (RR=1.05, 95% CI=1.01, 1.09).

Discussion

This unique cohort of women with biological measures from childhood into post-reproductive years allowed us to examine the impact of pregnancy with and without GDM on long-term metabolic health. First, we found that in childhood and adolescence – before any pregnancies – mean plasma glucose level was slightly higher among women who would go on to develop GDM compared to those who would become pregnant but never experience GDM, although the difference did not reach statistical significance in our data. Previous research has found elevated pre-pregnancy fasting glucose associated with significantly increased odds of GDM,[18, 19] suggesting preconceptional underpinnings of metabolic dysfunction in cases of GDM. Interestingly, we found that women who were nulligravid through their 40s had the highest childhood and adolescence mean fasting plasma glucose levels. It may be that these women experienced factors associated with both elevated glucose levels and infertility – polycystic ovary syndrome, for example.[20] Two of the 37 nulligravid women in this sample reported a history of polycystic ovarian syndrome.

Second, we found that nulligravid women and gravid women without a history of GDM had the same fasting plasma glucose levels in later life. Compared to both of those groups, women with a history of GDM, however, had significantly elevated fasting plasma glucose in later life, and an almost four-fold increase in risk of prediabetes. This corresponds to the well-established link between GDM and risk T2DM in later life.[12] The lack of difference in plasma glucose or pre-diabetes risk between nulligravid and gravid without GDM women further implicates pregnancy as a trigger revealing undetected pathologies as opposed to the cause in and of itself.[21] A previous study found that even slight glucose intolerance during pregnancy – regardless of GDM diagnosis – independently increased risk for future atherosclerotic morbidity.[22]

The test for heterogeneity by race suggested that association were similar but of greater magnitude among NH black women. There was no racial difference in early-life glucose levels in this sample (mean [SD]=83.9 [6.8] and 84.7 [6.7], respectively), nor between nulligravid and gravid NH black women regardless of GDM status. GDM was more frequently reported by gravid NH white women (14.6%) compared to gravid NH black women (9.3%), but obesity after age 40 was more common among NH black women (56% vs. 41%). Racial/ethnic differences in the contribution of BMI status to risk of GDM (and subsequent T2DM) suggest that a greater proportion of GMD cases among NH blacks are attributable to overweight and obesity compared to the proportion of cases among NH whites.[23] The added detrimental effects of obesity may explain exacerbated later-life plasma glucose differences between GDM cases and nulligravid women among NH blacks compared to NH whites.

This study benefits greatly from the availability of biologic measures from both pre- and post-reproductive years in a sample of women with varied reproductive histories. It is limited, however, by self-reported lifetime history of GDM. While almost all women (97%) gave permission to access medical records, only 16 had records available.. Many births occurred prior to widespread implementation of electronic medical records in Louisiana and records may have been destroyed as typical hospital policy is to retain records for 10 years

but not longer. Sample size restraints limited our ability to examine incidence of T2DM as an outcome, which may have provided more clinically-relevant evidence than plasma glucose levels alone. This a limitation that may be overcome in future analyses as the cohort continues to age. Finally, the racial/ethnic composition of our cohort was limited to NH black and white women only, prohibiting the investigation of glucose variation across a more diverse population.

Despite its limitations, this analysis contributes to the small amount of literature on women's health across the life course. The implications of our findings include the importance of targeted interventions for women aimed at monitoring and reducing glucose levels before, during, and in particular after pregnancy among women who develop GDM to ensure optimal health in aging for all women.

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References

1. DeSisto CL , Kim SY , Sharma AJ . Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007-2010 *Prev Chronic Dis.* 2014 6 19;11:E104. doi: 10.5888/pcd11.130415. PubMed PMID: ; PubMed Central PMCID: PMC4068111.24945238
2. Lavery JA , Friedman AM , Keyes KM , et al. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010. *BJOG.* 2016 8 11. doi: 10.1111/1471-0528.14236. PubMed PMID: ; eng.27510598
3. Wendland EM , Torloni MR , Falavigna M , et al. Gestational diabetes and pregnancy outcomes--a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria [Research Support, Non-U.S. Gov't Review]. *BMC Pregnancy Childbirth.* 2012 3 31;12:23. doi: 10.1186/1471-2393-12-23. PubMed PMID: 22462760; PubMed Central PMCID: eng.22462760
4. Bryson CL , Ioannou GN , Rulyak SJ , et al. Association between gestational diabetes and pregnancy-induced hypertension [Research Support, U.S. Gov't, Non-P.H.S.]. *Am J Epidemiol.* 2003 12 15;158(12):1148-53. PubMed PMID: ; eng.14652299
5. Kuh D , Ben-Shlomo Y , Lynch J , et al. Life course epidemiology. *J Epidemiol Community Health.* 2003 Oct;57(10):778-83. PubMed PMID: ; PubMed Central PMCID: PMC1732305.14573579
6. Leon MG , Moussa HN , Longo M , et al. Rate of Gestational Diabetes Mellitus and Pregnancy Outcomes in Patients with Chronic Hypertension. *Am J Perinatol.* 2016 2 18. doi: 10.1055/s-0036-1571318. PubMed PMID: .26890438
7. Chuang CH , Velott DL , Weisman CS . Exploring knowledge and attitudes related to pregnancy and preconception health in women with chronic medical conditions. *Matern Child Health J.* 2010 9;14(5):713-9. doi: 10.1007/s10995-009-0518-6. PubMed PMID: ; PubMed Central PMCID: PMC2924436.19760164
8. Baumfeld Y , Novack L , Wiznitzer A , et al. Pre-Conception Dyslipidemia Is Associated with Development of Preeclampsia and Gestational Diabetes Mellitus. *PLoS One.* 2015;10(10):e0139164. doi: 10.1371/journal.pone.0139164. PubMed PMID: ; PubMed Central PMCID: PMC4599807.26452270
9. Zhang S , Ding Z , Liu H , et al. Association between mental stress and gestational hypertension/preeclampsia: a meta-analysis. *Obstet Gynecol Surv.* 2013 12;68(12):825-34. doi: 10.1097/OGX.000000000000001. PubMed PMID: .25102019

10. Schummers L , Hutcheon JA , Bodnar LM , et al. Risk of adverse pregnancy outcomes by prepregnancy body mass index: a population-based study to inform prepregnancy weight loss counseling. *Obstet Gynecol.* 2015 1;125(1):133–43. doi: 10.1097/AOG.0000000000000591. PubMed PMID: ; PubMed Central PMCID: PMC4285688.25560115
11. Metsala J , Stach-Lempinen B , Gissler M , et al. Risk of Pregnancy Complications in Relation to Maternal Prepregnancy Body Mass Index: Population-Based Study from Finland 2006–10. *Paediatr Perinat Epidemiol.* 2016 1;30(1):28–37. doi: 10.1111/ppe.12248. PubMed PMID: . 26447743
12. Bellamy L , Casas JP , Hingorani AD , et al. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis [Meta-Analysis Research Support, Non-U.S. Gov't]. *Lancet.* 2009 5 23;373(9677):1773–9. doi: 10.1016/S0140-6736(09)60731-5. PubMed PMID: ; eng. 19465232
13. Williams D Pregnancy: a stress test for life [Review]. *Curr Opin Obstet Gynecol.* 2003 12;15(6): 465–71. doi: 10.1097/01.gco.0000103846.69273.ba. PubMed PMID: ; eng.14624211
14. Kessous R , Shoham-Vardi I , Pariente G , et al. An association between gestational diabetes mellitus and long-term maternal cardiovascular morbidity. *Heart.* 2013 8;99(15):1118–21. doi: 10.1136/heartjnl-2013-303945. PubMed PMID: .23749791
15. Kaul P , Savu A , Nerenberg KA , et al. Impact of gestational diabetes mellitus and high maternal weight on the development of diabetes, hypertension and cardiovascular disease: a population-level analysis. *Diabet Med.* 2015 2;32(2):164–73. doi: 10.1111/dme.12635. PubMed PMID: . 25407209
16. Tobias DK , Gaskins AJ , Missmer SA , et al. History of infertility and risk of type 2 diabetes mellitus: a prospective cohort study [Research Support, N.I.H., Extramural Research Support, N.I.H., Intramural Research Support, Non-U.S. Gov't]. *Diabetologia.* 2015 4;58(4):707–15. doi: 10.1007/s00125-015-3493-z. PubMed PMID: ; PubMed Central PMCID: PMC4416980. eng. 25596853
17. Berenson GSM CA ; Voors AW , Webber LS ; Shrinivasan SR ; Frank GC ; Foster TA ; Blonde CV Cardiovascular Risk Factors in Children: the Early Natural History of Atherosclerosis and Essential Hypertension. New York, NY: Oxford University Press; 1980.
18. Gunderson EP , Quesenberry CP , Jacobs DR , et al. Longitudinal study of prepregnancy cardiometabolic risk factors and subsequent risk of gestational diabetes mellitus: The CARDIA study [Multicenter Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Am J Epidemiol.* 2010 11 15;172(10):1131–43. doi: 10.1093/aje/kwq267. PubMed PMID: ; PubMed Central PMCID: PMC3004767. eng.20929958
19. Hedderson MM , Darbinian JA , Quesenberry CP , et al. Pregravid cardiometabolic risk profile and risk for gestational diabetes mellitus [Research Support, Non-U.S. Gov't]. *Am J Obstet Gynecol.* 2011 7;205(1):55 e1–7. doi: 10.1016/j.ajog.2011.03.037. PubMed PMID: ; eng.21620361
20. Azziz R , Carmina E , Chen ZJ , et al. Polycystic ovary syndrome. *Nature Reviews Disease Primers.* 2016 8 11;2. doi: Artn 16057 10.1038/Nrdp.2016.57. PubMed PMID: ISI: 000381373100001; English.
21. Wen SW , Xie RH , Tan H , et al. Preeclampsia and gestational diabetes mellitus: Pre-conception origins? *Medical Hypotheses.* 2012 7;79(1):120–125. doi: 10.1016/j.mehy.2012.04.019. PubMed PMID: ISI:000305375600031; English.22541860
22. Charach R , Wolak T , Shoham-Vardi I , et al. Can slight glucose intolerance during pregnancy predict future maternal atherosclerotic morbidity? *Diabet Med.* 2016 7;33(7):920–5. doi: 10.1111/dme.13036. PubMed PMID: .26606683
23. Kim SY , England L , Sappenfield W , et al. Racial/Ethnic Differences in the Percentage of Gestational Diabetes Mellitus Cases Attributable to Overweight and Obesity, Florida, 2004–2007. *Prev Chronic Dis.* 2012 4;9. doi: Artn 110249 10.5888/Pcd9.110249. PubMed PMID: ISI: 000306647200009; English.

Figure 1. Identification of the analytic sample.

Flowchart depicting number of women retained in the analytic sample based on availability of data on reproductive history and glucose concentrations.

Table 1.

Characteristics of the study population by pregnancy history (n=358).

	Whole sample (n=358)	Never pregnant (n=37, 10.3%)	Pregnant without gestational diabetes (n=280, 78.2%)	Pregnant with gestational diabetes (n=41, 11.5%)	P-value
Race	n (%)	n (%)	n (%)	n (%)	0.08
Black	114 (31.8)	7 (18.9)	97 (34.8)	10 (24.4)	
White	244 (68.2)	30 (81.1)	182 (65.2)	31 (75.6)	
BMI at age 40 or later					0.22
Underweight or normal weight (<25 kg/m ²)	93 (26.0)	14 (37.8)	72 (25.8)	7 (17.1)	
Overweight (25–29.9 kg/m ²)	100 (27.9)	10 (27.0)	79 (28.3)	10 (24.4)	
Obese (>30 kg/m ²)	165 (46.1)	13 (35.1)	128 (45.9)	24 (45.5)	
Prediabetes at age 40 or later (glucose ≥ 100 mg/dL)					<0.01
Yes	63 (17.6)	5 (13.5)	42 (15.0)	16 (39.0)	
No	296 (82.5)	32 (86.5)	238 (85.0)	25 (61.0)	
	Mean (Std)	Mean (Std)	Mean (Std)	Mean (Std)	
Parity, n	2.3 (1.4)	0	2.5 (1.2)	2.9 (1.3)	
Age at outcome measure, years	42.9 (1.5)	42.7 (1.4)	42.9 (1.6)	42.5 (1.5)	0.28
Mean pre-pregnancy glucose, (mg/dL)	84.5 (6.7)	88.7 (6.2)	83.9 (6.7)	84.6 (5.6)	<0.01
Mean post-pregnancy glucose (age 40 or older), (mg/dL)	93.7 (30.5)	89.5 (18.7)	91.3 (23.9)	114.2 (59.7)	<0.01

Table 2.

Model results predicting glucose at age 40+.

	Whole sample (n=358)			Stratified models		
	Crude model		Adjusted model	Black women (n=114)		White women (n=244)
	Beta	95% CI	Beta	95% CI	Beta	95% CI
Pregnancy History						
<i>Never Pregnant</i>	Ref		Ref		Ref	
<i>Ever pregnant without gestational diabetes</i>	1.77	-8.39 11.94	5.42	-6.30 17.13	11.10	-22.56 44.77
<i>Ever pregnant with gestational diabetes</i>	24.78	11.60 37.95	26.99	12.35 41.64	64.47	21.32 107.62
Pre-pregnancy glucose						
			0.87	0.42 1.32	1.27	0.20 2.34
Parity			-0.87	-3.44 1.70	-0.24	-5.68 5.20
BMI						
<i>Underweight or normal weight</i>			Ref		Ref	
<i>Overweight</i>			4.74	-3.25 12.72	6.98	-15.26 29.21
<i>Obese</i>			14.66	7.39 21.93	15.60	-4.33 35.52
Race						
<i>White</i>			Ref		Ref	
<i>Black</i>			9.11	2.69 15.54		
Age at outcome measure			-1.24	-3.13 0.65	-1.37	-5.82 3.08
					-1.71	-3.67 -0.05