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Karen A. Scott Date

The Association of Immigrant Status, Preeclampsia, and Gestational Age at Delivery among Black Women with Diabetes in California

By

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The Association of Immigrant Status, Preeclampsia, and Gestational Age at Delivery among Black Women with Diabetes in California

By

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Doctor of Medicine
Case Western Reserve University School of Medicine
2002

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An abstract of
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Rollins School of Public Health of Emory University
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Abstract

The Association of Immigrant Status, Preeclampsia, and Gestational Age at Delivery among Black Women with Diabetes in California
By Karen A. Scott, MD

Purpose: Black women are at higher risk for pregestational diabetes (PGDM), gestational diabetes (GDM), and preterm birth (PTB, < 37 completed weeks' gestation). Foreign-born women have lower risk of PTB. We examined associations between immigrant status, maternal, social, and obstetric characteristics, and risk of PTB among Black women with any diabetes.

Methods: From 3,160,268 California live births, 2007-2012, we assessed 7,024 singleton PTBs or full term births (39-40 weeks) from non-Hispanic Black (NHB) diabetic women. We examined crude (cOR) and adjusted odds ratios (aOR) with stepwise backward logistic regression and 95% confidence intervals (CIs).

Results: Foreign-born status was associated with a lower risk of PTB [OR 0.51 (95% CI 0.43, 0.61)]. U.S.-born women, compared to Foreign-born women, were more likely to have some characteristics associated with PTB (< 25 years of age, < 12 years of education, Medicaid-paid delivery, uterine tract infection (UTI), smoking, preeclampsia, and obesity (BMI >30). The greatest cORs for PTB were for preeclampsia [7.52(6.41, 8.83)], smoking [1.67(1.42, 1.96)], and obesity [1.22(1.05, 1.40)]. After adjustment, aOR for PTB among Foreign-born births was 0.56(0.44, 0.71).

Conclusions: Foreign-born status is protective of PTB among NHB diabetic women. Further research is needed on preeclampsia, smoking, obesity, and structural racism.

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CHAPTER I

INTRODUCTION

In the United States, diabetes affects nearly 6%-7% of all pregnancies, with a similar prevalence of 7.6% in the state of California [1]. Nearly 85% of diabetes in pregnancy is a result of gestational diabetes mellitus (GDM) [2-4], a type of glucose intolerance that is first recognized at the onset of or during pregnancy. The remaining cases of diabetes in pregnancy are pre-gestational diabetes (PGDM) [5], including both type 1 and type 2 diabetes mellitus (DM). GDM is associated with the subsequent development of serious health consequences for mother and child, including development or worsening end organ damage affecting eyes, kidneys, intestines, and blood vessels; hypertension and preeclampsia; and cardiovascular disease such as congestive heart failure and ischemic coronary syndrome; and ketoacidosis. Women with GDM are also at increased risk for preterm births (PTBs), cesarean section, stillbirths, and worsening glucose intolerance requiring insulin treatment [6-8]. Fetal complications such as spontaneous miscarriage and congenital anomalies can occur early in pregnancy [9]. Additional fetal co-morbidities include increased risk for intrauterine growth restriction, especially with a simultaneous development of hypertension [10], macrosomia (more specifically fetal adiposity) [11], and intrauterine fetal death [12]. Newborns of GDM women are at higher risks of hypoglycemia, polycythemia, hypocalcemia, hyperbilirubinemia, cardiac dysfunction secondary to septal hypertrophy, and respiratory distress syndrome [13]. Long-term effects of GDM include increased risk of Type II DM for women [14] and obesity in childhood and early adulthood for their offspring [15].

Previous studies established cigarette smoking as a risk factor for Type 2 DM but available studies that examined smoking and GDM are scarce and conflicting, predominantly conducted in non-Hispanic white women [16]. Compared to Non-Hispanic Black (hereinafter abbreviated as Black) women without GDM, Black women with new onset of GDM may be significantly older, of higher gravidity, more obese, with more rapid weight gain, a family history of diabetes, and diagnosed with more hypertension during the index pregnancy [17]. Compared to non-Hispanic white (hereinafter abbreviated as white), Black women may have both a higher prevalence and incidence of GDM [18], although study findings are conflicting [19-22], possibly because of differences in other pregnancy risk factors such as age and obesity. In the U.S. today, Black women have the highest rates of PGDM [23] and preterm birth (PTB, < 37 completed weeks' gestation) [24-26], yet the epidemiology of PGDM and GDM among Black women, including the magnitude of their effect on PTB, remains largely unexplored.

Women born outside of the U.S. were historically more likely than U.S.-born women to have GDM, mainly owing to their older childbearing age. However, adjusted diabetes risk remains elevated for Asian-Indian, Black, Filipino, Puerto Rican, and Central and South American foreign-born women. Conversely, birthplace outside the U.S. significantly reduces diabetes risk for Japanese, Mexican, and Native American women [27]. Past population-based studies have evaluated the associations between maternal race/ethnicity, educational attainment, and risk of pregnancy complications and adverse birth outcomes [28] and the role of obesity in the risk of GDM between pregnant women based on immigrant status [29]. Foreign birth is an additional risk factor for GDM [30] among Blacks in the U.S. The elevated risk was explained by older childbearing age of

immigrant women. Age adjusted diabetes risk remained elevated for many minority foreign born groups, including Blacks [31].

Some risk factors for PTB and PGDM overlap, including association with higher levels of specific inflammatory markers [32-39]. Women with a prior PTB have pre-existing, possibly long-standing history of low-grade inflammation [40-42], a predictor for subsequent development of type 2 DM. Such associations suggest PTB may represent a signal for elevated inflammatory markers that may facilitate the postpartum development of type 2 diabetes, among both predominantly white and Black populations [43-44]. PTB may also be an indicator of vascular dysfunction, since PTB is associated with type 2 DM among women without GDM or hypertensive disorders of pregnancy [45]. These associations appear to be independent of maternal weight gain or obesity [46]. Thus, previous studies highlight the need for additional research to examine the relationships between diabetes, preeclampsia and PTB among Black women.

Risk of PTB and GDM differ in one notable risk factor, namely immigration status. Foreign-born Black women are less likely than U.S.-born women to experience PTB [47-50], although they may be more likely to develop GDM. In the U.S., country of birth may proxy the impact of structural and life course experiences of racial discrimination [51-55]. To date, no studies exist on the association between the country of birth and risk of PTB among Black women with diabetes. To address this gap, we examined the relationships between immigrant status, maternal, social, and obstetric characteristics, and risk of PTB among Black women with any diabetes.

CHAPTER II

The Association of Immigrant Status, Preeclampsia, and Gestational Age at Delivery among Black Women with Diabetes in California

INTRODUCTION

In the United States, diabetes affects 6%-7% of all pregnancies, with a prevalence of 7.6% in the state of California [56]. Nearly 85% of diabetes in pregnancy is a result of gestational diabetes mellitus (GDM) [57-59], a type of glucose intolerance that is first recognized at the onset of or during pregnancy. The remaining cases of diabetes in pregnancy are pre-gestational diabetes (PGDM) [60], including both type 1 and type 2 diabetes mellitus (DM). Based on 2014 data, Black women are about twice as likely as white women to be diagnosed with DM, based on age-adjusted prevalence of DM per 100 population (9.9 and 5.3) [61]. According to an examination of temporal trends from 1989 through 2004, the prevalence of GDM among Black women increased by 172% from 1990 to 2004 (1.5-4.1%) compared to an 80% increase observed among white women in this time period (2-3.6%) [62]. GDM is associated with the subsequent development of serious health consequences for mother and child, including development or worsening end organ damage affecting eyes, kidneys, intestines, and blood vessels; hypertension and preeclampsia; and cardiovascular disease such as congestive heart failure and ischemic coronary syndrome; and ketoacidosis. Women with GDM are also at increased risk for adverse birth outcomes including preterm delivery (< 37 weeks of gestation).

Women born outside of the U.S. have been historically shown to be more likely than U.S.-born women to have GDM, mainly owing to their older childbearing age [63].

However, adjusted diabetes risk remains elevated for Black, foreign-born women [64]. Past evidence from population-based studies have evaluated the associations between maternal race/ethnicity, educational attainment, and risk of pregnancy complications and adverse birth outcomes [65] and the role of obesity in the risk of GDM between pregnant women based on immigrant status [66]. Foreign birth is an additional risk factor for GDM [67] among Blacks in the U.S. The elevated risk was explained by older childbearing age of immigrant women. Age adjusted diabetes risk remained elevated for many minority foreign born groups, including Blacks [68].

Some risk factors for preterm birth (PTB) and PGDM overlap, including association with higher levels of specific inflammatory markers [69-76]. Women with a prior PTB have pre-existing, and a possibly long-standing history of low-grade inflammation [77-80], a predictor for subsequent development of type 2 DM. Such associations suggest PTB may represent a signal for elevated inflammatory markers that may facilitate the postpartum development of type 2 diabetes, among both predominantly white and Black populations [81-82]. Risk of PTB and GDM differ in one notable risk factor, namely immigration status. Foreign-born Black women are less likely than U.S.-born women to experience PTB [83-86] although they may be more likely to develop GDM. In the U.S., country of birth may proxy the impact of structural and life course experiences of racism [87-91]. To date, no data exist on the association between the country of birth and risk of PTB among Black women with diabetes. To address this gap, we examined the relationships between immigrant status, maternal, social, and obstetric characteristics, and risk of PTB among Black women with any diabetes.

MATERIALS AND METHODS

Study population

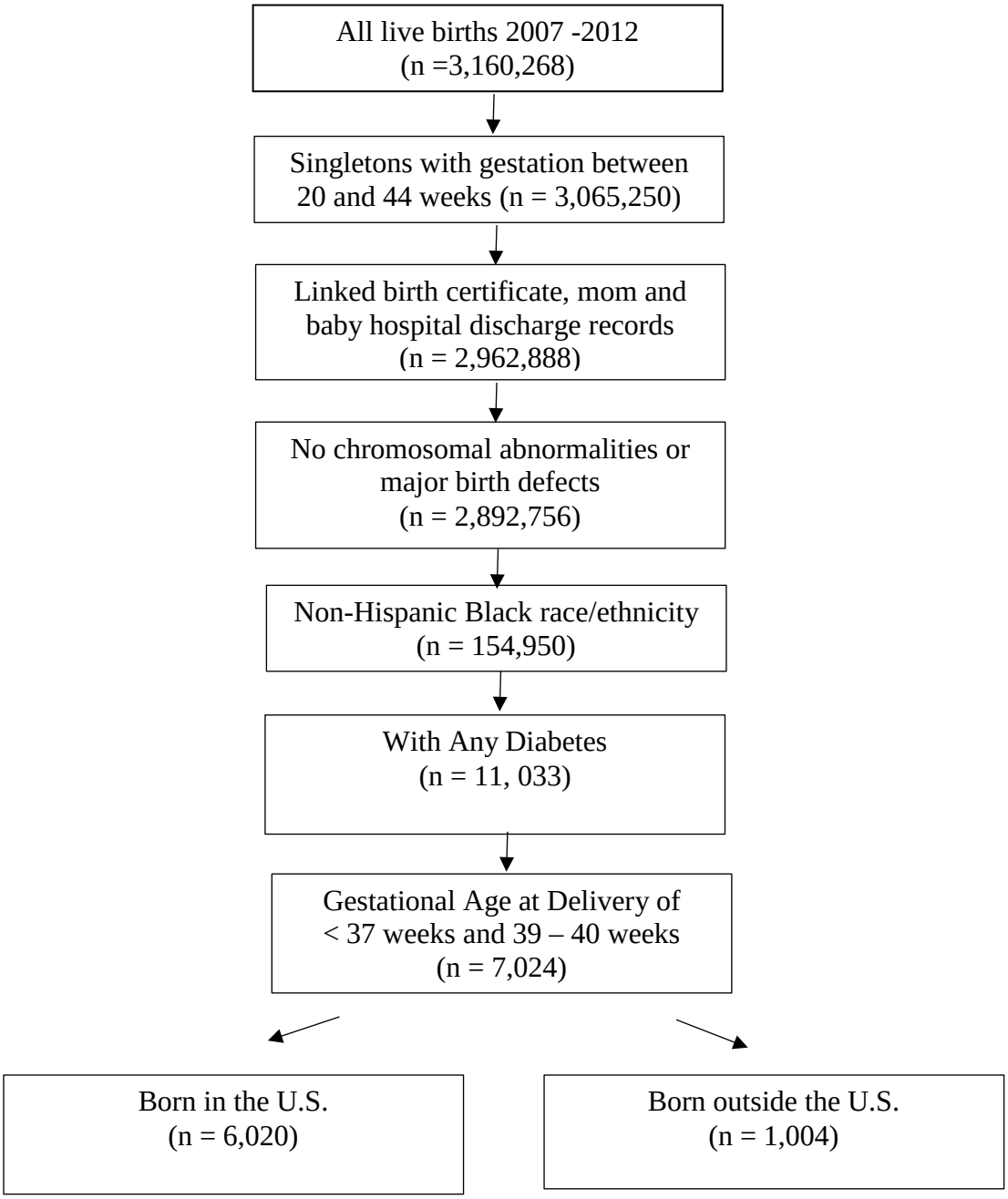
From a population of 3,160,268 California live births, 2007 – 2012, we selected 7,024 non-Hispanic Black women with PGDM or GDM, whose delivery was preterm (cases, < 37 weeks) or full-term (controls, 39-40 weeks) [92]. We excluded infants with chromosomal abnormalities or major birth defects and limited the sample to women whose birth certificates were linked with mom and baby hospital discharge records. Figure 1 describes the sample selection process.

Measures

Birth certificate data included self-defined maternal country of birth (hereinafter referred to as immigrant status), the best obstetric estimate of gestation at birth, maternal age at birth (<20, 20-24, 25-34, 35-39, and 40 years and older), obesity [maternal body mass index (BMI)] at onset of pregnancy based (maternal height and prepregnancy weight in kg/m^2 where BMI $\geq$ 30 or non-obesity BMI <30), smoking during pregnancy (yes/no), payer status for delivery [private or Medi-Cal (California's Medicaid program or state funded health insurance for low income individuals)], maternal education (<12, 12, and > 12 years), participation in women, infant, and children's (WIC) program (yes/no), and month of prenatal care initiation (< 5 months or $\geq$ 5 months or none). We used International Classification of Disease, 9^{th} Revision, Clinical Modification [93-94] codes to classify PGDM (ICD-9 codes 648.0 and 250.0), GDM (648.8), and obstetric characteristics including preeclampsia, mild, severe or unspecified (642.4 and 642.5) and with or without pre-existing hypertension (642.7) [95] history of prior PTB (yes/no), and

urinary tract infection (UTI) (yes/no). Hospital discharge records included information on the obstetric characteristics based on ICD-9 codes.

Figure 1. Sample Selection



Statistical methods

We performed univariate and bivariate comparisons of gestational delivery week using chi-square analysis between U.S.-born (the referent group) and foreign-born Black women. We also conducted bivariate logistic regression to calculate the crude odds ratios (cORs) and 95% confidence intervals (CIs) for the associations of immigrant status and gestational duration adjusted individually by maternal, social, and obstetric characteristics. In addition, we performed multiple logistic regression analyses to calculate the adjusted odds ratios (aORs) and 95% CIs for the association between immigrant status and PTB with maternal, social, and obstetric factors as potential covariates.

We determined the presence of effect modification by calculating stratum-specific estimates of associations between covariates and PTB using the Breslow-Day test for homogeneity of the odds ratios with statistical significance, $p < 0.05$. In the preliminary analysis, we assessed for the presence of interaction between foreign-born Black women and education to determine whether to develop a new variable that incorporated education.

To assess for confounding, we obtained the cORs, aORs, and standard Wald 95% CIs for differences in delivery timing by these covariates between immigrant status groups. If the magnitude of adjusted association changed by 10% or more, we included the potential confounder in the final model. We used backward stepwise regression (using criteria $p=0.1$ to enter the model and $p=0.05$ to remain in the model) for final model building, with inclusion of potential covariates chosen either in preliminary analyses or by literature review. To assess model adequacy, we performed the Hosmer-Lemeshow (H-L) goodness of fit test wherein if the H-L test demonstrated sufficient evidence to reject the null hypothesis with a p value > 0.05, it indicated a good model fit.

We used Statistical Analysis Software version 9.4 (Cary, NC) to analyze data received by the California Preterm Birth Initiative at the University of California San Francisco as of June 21, 2016. Methods and protocols for the study were approved by the Committee for the Protection of Human Subjects within the Health and Human Services Agency of the State of California, as well as Emory University.

RESULTS

Most (85.7%) women were born in the U.S. In comparison to U.S.-born women, foreign-born women were more likely to be older, possess a bachelor's degree or higher, use private insurance for delivery, and initiate prenatal care prior to 5 months' gestation (Table 1). U.S.-born women were more likely to be young, to have had a prior PTB, less-educated, to participate in WIC, use Medi-Cal for delivery, initiate prenatal care at $\geq$ 5 months or not at all, to have a UTI, to smoke, to develop preeclampsia, and be obese (Table 1). Compared with U.S.-born women, foreign-born women had half the risk of PTB [cOR 0.51 (95% CI 0.43, 0.61)] (Table 2). Maternal age $\geq$ 35 years, use of Medi-Cal, prior PTB, UTI, preeclampsia, smoking, and obesity were significantly associated with higher risk of PTB. The highest odd ratios for PTB were preeclampsia, smoking, and prior PTB (among multiparous women).

Table 1. Distribution of maternal, social, and obstetric sample characteristics by immigrant status, N=7024

	U.S.-Born n=6020	Foreign-Born n=1004	χ^2	p value
	n (%)	n (%)		
Maternal Age (years)				
<20	295(4.90)	7(0.07)		
20-24	1105(18.36)	45(4.48)		
25 – 34	3195(53.07)	530 (52.79)	249.55	p<.0001
35 – 39	1051(17.46)	297(29.58)		
≥ 40	374(6.21)	125(12.45)		
Missing values				
Prior PTB				
Yes	148(2.46)	17(1.69)	3.43	p=0.1796
No	3844(63.85)	664(66.14)		
Missing (including nulliparous)	2028(33.69)	323(32.17)		
Education				
< 12	708(11.76)	70(6.97)	54.51	p<.0001
12	1910(31.73)	256(25.50)		
≥ 12	3268(54.29)	636(63.35)		
Missing values	134(2.23)	42(4.19)		
Participation in WIC				
Yes	3975(66.03)	493(49.10)		
No	1956(32.49)	495(49.30)	108.52	p<.0001
Missing values	89(1.48)	16(1.59)		
Payer for delivery				
Medical	3182(52.86)	453(45.12)		
Private	2476 (41.13)	488(48.61)	21.45	p<.0001
Missing values	362(6.01)	63(6.27)		
Month of prenatal care initiation				
< 5 months	5295(87.96)	902(89.84)	6.88	p = 0.0321
≥5 months or none	567(9.42)	89(8.86)		
Missing values	158(2.62)	13(1.29)		

Table 1 Continued

	U.S.-Born n=6020	Foreign-Born n=1004	χ^2	p value
	n (%)	n (%)		
Urinary Tract Infection Yes No Missing values	855(12.17) 5165(85.80)	45(4.48) 959(95.52)	72.78	p<.0001
Preeclampsia Yes No Missing values	707(11.74) 5313(88.26)	76(7.57) 928(92.43)	15.14	p<.0001
Smoking during pregnancy Yes No Missing values	714(11.86) 5306(88.14)	23(2.29) 981(97.71)	83.91	p<.0001
Body mass index [BMI (kg/m^2)] < 30 ≥30 Missing values	1162(19.30) 2978(49.47) 1880(31.23)	342(34.06) 259(25.80) 403(40.14)	213.21	p<.0001

No covariables confounded the relationship between foreign-born status and PTB (Table 3). However, covariables were included in regression analysis to assess joint effects and potential interactions. The interaction between immigrant status and obesity was significant (p=0.0073). Both obese and non-obese foreign-born women had reduced odds ratios for PTB. Although the point estimate for obese women was closer to the null, it remained significant with p=0.0318 (data not shown). Similarly, both obese and non-obese U.S.-born women had increased odds ratios for PTB. Although the point estimate for obese women was closer to the null, it remained significant with p=0.0318 (data not shown). After adjusting for other covariates, this interaction was no longer significant. After stepwise backward regression analyses, covariates in the final model include prior

PTB, maternal age, education, UTI, smoking, and preeclampsia. The H-L test demonstrated sufficient evidence to reject the null hypothesis, confirming a good fit, with a p value = 0.9103. We found that the protective association of foreign birth was only slightly attenuated when adjusted for potential confounding and effect modification [aOR 0.56(0.44, 0.71). Table 4].

Table 2. Comparison of maternal, social, and obstetric characteristic by gestational duration.

	< 37 weeks n=1778	39 – 40 weeks n=5246	cOR (95% CI)	p value
	n (%)	n (%)		
Immigrant Status				
US-Born	1619(91.06)	4401(83.89)	Reference	
Foreign-Born	159(8.94)	845(16.11)	0.51(0.43,0.61)	p <0.0001
Maternal Age (years)				
<20	56(3.15)	246(4.69)	0.69(0.51,0.94)	
20-24	281(15.80)	869(16.57)	0.99(0.84,1.15)	
25 – 34	921(51.80)	2804(53.45)	Reference	p = 0.0007
35 – 39	365(20.53)	983(18.74)	1.13(0.98,1.30)	
≥ 40	155(8.72)	344(6.45)	1.37(1.12,1.68)	
Missing values				
Education				
< 12	222(12.49)	556(10.60)	1.20(1.00,1.437)	
12	542(30.48)	1624(30.96)	Reference	p = 0.0766
≥ 12	964(54.22)	2940(56.04)	0.98(0.87,1.11)	
Missing values	50(2.92)	126(2.40)		
Participation in WIC				
Yes	1113(62.60)	3355(63.95)	0.95(0.84,1.06)	p=0.3235
No	637(35.83)	1814(34.58)	Reference	
Missing values	28(1.57)	77(1.47)		
Payer for delivery				
Medical	960(53.99)	2675(50.99)	1.14(1.020,1.277)	p=0.0207
Private	709(39.88)	2255(42.99)	Reference	
Missing values	109(6.13)	316(6.02)		

Table 2 Continued

	< 37 weeks n=1778	39 – 40 weeks n=5246	cOR (95% CI)	p value
	n (%)	n (%)		
Month of prenatal care initiation				
< 5 months	1578(88.75)	4619(88.05)	Reference	p=0.1231
≥5 months	149(8.38)	507(9.66)	0.86(0.71,1.04)	
Missing values	51(2.87)	120(2.32)		
Prior PTB				
Yes	99(5.57)	66(1.26)	4.721(3.43,6.49)	p<0.0001
No	1087(61.14)	3421(65.21)	Reference	
Missing values	592(33.30)	1759(33.53)		
Preeclampsia				
Yes	514(28.91)	269(5.13)	7.52(6.41,8.83)	p<0.0001
No	1264(71.09)	4977(94.87)	Reference	
Missing values	0(0)	0(0)		
Smoking during pregnancy				
Yes	256(14.40)	481(9.17)	1.67(1.42,1.96)	p<0.0001
No	1522(85.60)	4765(90.83)	Reference	
Missing values	0(0)	0(0)		
Body mass index [BMI (kg/m^2)]				
< 30	350(19.69)	1154(22.0)	Reference	
≥30	872(49.04)	2365(45.08)	1.22(1.05,1.40)	p=0.0073
Missing values	556(31.27)	1727(32.92)		

Table 3. Associations of immigrant status and gestational duration adjusted individually by maternal, social, and obstetric characteristics.

	OR (95% CI)
Immigrant Status US-Born Foreign-Born	cOR (95% CI) 1.00 0.51(0.43,0.61)
US-Born Foreign-Born Controlling for Prior PTB *(n) = 4673*	aOR(95% CI) 1.00 0.53(0.43,0.66)
US-Born Foreign-Born Controlling for Maternal Age *(n) =7024*	aOR (95% CI) 1.00 0.47(0.40,0.57)
Immigrant Status US-Born Foreign-Born Controlling for Education *(n) =6848*	aOR (95% CI) 1.00 0.51(0.42,0.61)
US-Born Foreign-Born Controlling for Participation in WIC *(n) =6919*	aOR (95% CI) 1.00 0.50(0.41,0.60)
US-Born Foreign-Born Controlling for Medi-Cal *(n)=6599*	aOR (95% CI) 1.00 0.50(0.42,0.61)
US-Born Foreign-Born Controlling for Month of prenatal care initiation *(n) = 6853*	aOR (95% CI) 1.00 0.52(0.43,0.62)

Table 3 Continued

	OR (95% CI)
US-Born Foreign-Born Controlling for UTI *(n)=7024*	aOR (95% CI) 1.00 0.54(0.45,0.65)
US-Born Foreign-Born Controlling for Preeclampsia *(n)=7024*	aOR (95% CI) 1.00 0.54(0.45,0.65)
US-Born Foreign-Born Controlling for Smoking *(n)=7024*	aOR (95% CI) 1.00 0.54(0.45,0.64)
US-Born Foreign-Born Controlling for BMI *(n) = 4741*	aOR (95% CI) 1.00 0.53(0.42,0.66)

Table 4. Fully adjusted associations for PTB based on immigrant status., N=7,024

	Preterm Birth aOR (95% CI)*^
US-Born Foreign-Born *(n) = 4559*	1.00 0.56(0.44,0.71)
*Adjustment factors based on significant predictors of PTB and interactions (prior PTB, maternal age, UTI, smoking, preeclampsia, payer for delivery, education, obesity, and interaction between immigrant status and obesity). ^List of covariates remaining in the final model include prior PTB, maternal age, education, UTI, smoking, and preeclampsia, after stepwise backward regression analyses.	

DISCUSSION

Among singleton live births in California, 2007-2012, 16.1% of Black women with diabetes (1178 of 11033) experienced PTB. In this high-risk population, foreign-born women were only about half as likely to have a PTB as were U.S.-born women (cOR 0.51). The magnitude of this finding is greater than that reported for Black women in the U.S. in 2013, where 11.1% of U.S.-born and 7.9% of foreign-born Black women had a PTB [96]. Risk factors for PTB were different in the two populations; for example, U.S.-born, compared to foreign-born, women were at higher risks for being less educated, using Medi-Cal, smoking, and having pregnancy complications. After adjusting for these risk factors, the association of immigration status with PTB remained similar (aOR = 0.56), suggesting that these risk factors did not explain the protective effect of foreign birth. Our study supports a PTB disparity between U.S.-born and foreign-born Black women after adjustment for covariates, as demonstrated by Howard et al [97] and DeSisto et al [98]. Similarly, DeSisto et al. [99] concluded that the majority of PTB disparities examined for U.S.-born Black women compared to both foreign-born Black women and U.S.-born white women remained unexplained by the variables their model. Yet, the authors succeeded in identifying individual contributions to the PTB disparities and determined that paternal acknowledgement, maternal hypertension, and maternal education explained the largest proportion of the excess PTB rates among U.S.-born Black women compared to both foreign-born Black and U.S.-born white women [100].

Preeclampsia was the greatest overall risk factor for PTB in this sample (aOR = 7.52). It is possible that some preterm deliveries were indicated to treat preeclampsia. It is notable that 5.1% of women with full-term birth were preeclamptic, and perhaps some

of them should have had indicated deliveries prior to 39 weeks, based on 2013 guidelines issued by the American College of Obstetricians and Gynecologists (ACOG), after study completion date [101]. The large effect of preeclampsia risk for PTB, given no evidence of interaction between immigrant status and preeclampsia, suggests a potential role for unmeasured independent variables, such as stress or inflammation. Diabetes and preeclampsia may act synergistically through a common pathway of inflammation, where PTB may also be an indicator of vascular dysfunction [102], given the significant associations between UTI, preeclampsia, smoking and PTB. Our study findings support the review by Weissgerber and Mudd [103] which argues that: 1) preexisting diabetes is a risk factor for preeclampsia [104-105]; 2) obesity is a shared risk factor for preeclampsia and type 2 DM; and 3) preeclampsia persists as a risk factor among women with type 2 DM even when women are matched for BMI [106].

Strengths

This is the first study to evaluate the association of immigrant status and PTB in a high-risk population of Black women. The study's strengths include: 1) a large, population-based sample with a single racial group exclusive to Black women with any diabetes; 2) sufficient statistical power to adjust for important covariates; 3) birth certificates linked to hospital discharge data; 4) and evaluation of interactions between immigrant status and key variables, including preeclampsia, smoking, maternal age, and BMI.

Limitations

There were two primary limitations of this study: (1) an inability to delineate between medically indicated and spontaneous preterm births, as well as information on

how UTI was diagnosed and missing information on BMI for about one-third of the sample; and (2) no information to measure key variables associated with PTB and immigrant status such as marital status or partner relationship, pregnancy wantedness, and pregnancy-related stress.

Implications

Black women with diabetes remain at higher risk for PTB, despite presumed social protectors (i.e. health insurance, utilization of public resources, >12 years education, and initiation of prenatal care prior to 5 months). However, our study suggests that foreign-born status serves as a protective factor from PTB, independent of established risk factors even in women with DM. New, longitudinal research should focus on measures of acculturation, life course experience of structural and interpersonal racism and other stressors, biomarkers, and glycemic control.

In addition, given the strong associations between diabetes, preeclampsia, and PTB, we recommend future studies examine the relationships between intensity and type of medical management, PTB subtypes, including spontaneous and indicated, and development of preeclampsia in U.S- and foreign-born Black women with any diabetes. Studies are needed to explore the interactions between preeclampsia, smoking, obesity, and life stressors and their effect on delivery outcomes.

CONCLUSION

Foreign-born status is protective of PTB risk among Black women with diabetes, independent of other known risk factors. There is an urgent need for advanced epidemiological research to identify the underlying causes of excess PTB among U.S.-born women. Our study serves as a building block for epidemiologists, clinicians, and clinician

scientists and suggests that PTB may be in part due to chronic inflammation or vasculature dysfunction in response to chronic life stressors. Our findings may support the need for randomized trials to assess pharmacologic interventions such as 17-hydroxyprogesteone (17P, for women with history of recurrent preterm birth) and baby aspirin (for women with a history of early onset preeclampsia and prior preterm birth less than 34 completed gestational weeks), particularly among Black women with any diabetes, aged >35 years or older, obese, and other significant personal and family history. Furthermore, our study supports investment in evidence-based approaches such as doula support and group prenatal and pediatric care throughout pregnancy, birth, and beyond, as means to mitigate the adverse impact of structural and life experiences of racism on maternal health, health care experiences, and quality of care.

CHAPTER III

DISCUSION

In our study, we observed that foreign-born Black women with diabetes are at decreased risk for PTB compared to U.S.-born women. Our study supports that there is a PTB disparity between U.S.-born and foreign-born Black women after adjustment for covariates, as demonstrated by Howard et al [107] and DeSisto et al [108]. Although 42% of foreign-born women in the study are older (≥35 years), and maternal age ≥35 is associated with PTB, foreign-born status remains protective. Foreign-born women in the cohort are also more educated, with higher utilization of private insurance and earlier initiation of prenatal care. In comparison, U.S.-born Black women with diabetes tend to be younger; nearly 1 in 4 (23.26%) women are < 25 years of age compared to 1 in 22 (4.55%) foreign-born women. However, maternal age < 20 years remains protective against PTB while U.S.-born status remains significantly associated with PTB. U.S.-born Black women are also more likely to smoke, to be diagnosed with UTI, and to develop preeclampsia. Possible explanations for the differences in PTB could be that older, more educated, and privately insured foreign-born women may possess higher health literacy and therefore assert greater autonomy during health care communication and decision-making.

Prior evidence has demonstrated that foreign-born Black women do not experience the same historical lifetime exposures to racism and trauma within the US context as U.S.-born Black women. However, the impact of structural racism may vary depending on the age at which foreign-born Black women migrated to the U.S. [109].

Foreign-born women may have greater acceptance, access, and utilization of prenatal services and possibly higher quality of care, based on their higher social and health capital. Previous studies have also confirmed that Black women from countries in Africa and the Caribbean are more likely to be in better physical health than U.S.-born Black women and to experience pregnancy-related and birth outcomes similar those found among white women in the U.S. [110-112]. Consequently, foreign-born Black women with diabetes may be receiving earlier and improved medical management of their PGDM or GDM, with possible improved glycemic control. Perhaps improved glycemic control in pregnancy results in lower rates of PTB, particularly among older higher socioeconomic status foreign-born Black women with diabetes. Since our study did not include measure of glycemic control, we can't make any inferences about the association between glycemic control and PTB. Our study found that neither initiation of prenatal care nor age confounded the relationship between immigrant status and PTB. There may be an independent variable, a potential modifier, confounder, or mediator, that was not examined in this study. Diabetic patients likely attend more prenatal visits for increased surveillance of mother, fetus, and placenta function, regardless of initiation of prenatal care. Thus, the adequacy of prenatal care utilization and glycemic control may serve as a potential modifier, confounder, or mediator. One study could measure the difference between adequacy of PNC utilization and glycemic control between U.S.-born and foreign-born Black women and determine whether that difference explains the difference in PTB risk among Black women diabetes.

Higher maternal education remained a significant protective factor for PTB among foreign-born Black women, a conclusion confirmed by DeSisto et al. [113]. One possible explanation for the differences could be that younger U.S-born Black women may not be as comfortable and confident in navigating the fragmented and complex U.S. health care system. Thus, they may not be as autonomous in health care communication, utilization, and decision making as the older foreign-born women. Also, younger U.S.-born women's reliance on public insurance may limit their access to high quality, coordinated prenatal care services. Subsequently, younger U.S.-born Black women may experience compounded levels of gender, race, and age discrimination impacting maternal autonomy and quality of care, including barriers to early and appropriate screening, diagnosis, and medical management, resulting in perhaps poor glycemic control or delayed care. Thus, U.S.-born women have higher risk of PTB resulting from preeclampsia.

Study findings revealed that the strongest predictors of PTB among Black women with diabetes were preeclampsia and previous PTB, respectively. The larger effect of preeclampsia on risk for PTB, given no evidence of interaction between immigrant status and preeclampsia, raises the possibility of independent variables not captured in the data analysis, such as stress or inflammation and differentiation between spontaneous versus medically indicated PTB. Among Black women with diabetes who experienced a PTB, nearly 1 in 3 (28.91%) also developed preeclampsia compared to 1 in 20 (5.13%) Black women who delivered at full term. Our analysis builds on current literature that supports the mechanism by which diabetes and preeclampsia synergistically act through a common pathway of inflammation, where PTB may be also be an indicator of vascular dysfunction [114], given the significant associations between UTI, preeclampsia, and smoking and

PTB. One possible explanation for the association of preeclampsia with PTB could be the severity of the preeclampsia and concomitant effect on the mother, worsening blood pressures and organ dysfunction; fetus, leading to growth restriction; and the placenta leading to uteroplacental insufficiency (i.e., abnormal blood flow through the uterine artery) or separation of the placenta from the uterine wall (i.e., placental abruption). Both adverse developments in the mother, fetus or placenta may result in a medically indicated PTB. A second explanation for the association between PTB and preeclampsia in our cohort could be attributed to the higher proportion of obese women in the PTB group compared to the term group (49.04% vs 45.0%, p=0.0073 and the higher proportion of obese women among U.S-born and foreign-born women (49.47% vs 25.80%, p<0.001.). Although the etiology of preeclampsia remains obscure, previous studies have identified maternal pre-pregnancy BMI as a vital independent risk factor in the development of preeclampsia [115-116]. A 2013 meta-analysis of nulliparous and multiparous women found being overweight or obese (BMI $\geq$ 25) had an approximately 2-4 fold increased risk of preeclampsia compared to normal weight women (BMI 20-24.9 kg/m^2) [117]. Perhaps, PTB is a product of the synergistic effects of obesity and diabetes in the presence of preeclampsia, and thus requires the examination of obesity or preeclampsia as a potential mediator of the immigrant status and PTB relationship.

Our study findings also support the review by Weissgerber and Mudd [118] that identified the unique challenges of studying preeclampsia in women with diabetes and highlighted recent reports examining the pathophysiology in women with type 1 or 2 diabetes. In addition, Weissgerber and Mudd [119] examined the relationship between GDM and preeclampsia and proposed a possible shared pathophysiology pathway for

preeclampsia and GDM. Salient points regarding associations include: 1) preexisting diabetes as a risk factor for preeclampsia [120-121]; 2) obesity as a shared risk factor for both preeclampsia and type 2 DM; and 3) persisting greater preeclampsia risk among women with type 2 DM even when women are matched for BMI [122].

Given the increased risk of developing preeclampsia among Black women and women with diabetes, there is a need to better understand if and how preeclampsia mediates the relationship between immigrant status and timing of delivery among Black women with diabetes. For women with mild gestational hypertension or preeclampsia without severe features at or beyond 37 weeks, the current clinical 2013 recommendations from ACOG is to deliver rather than continue observation [123]. Our study completion date was before the release of the 2013 ACOG clinical recommendations. Given that more than one-third of women with preeclampsia (269 of 783) delivered at 39-40 weeks, our findings suggest that a fuller examination of this question will require examination of the full gestational distribution of the Black diabetic women who had preeclampsia.

Our study did not find any significant associations between immigrant status, WIC, utilization of public health insurance, or maternal education and PTB, among a study cohort of U.S.- and foreign-born Black women with diabetes. Our study findings contribute significantly to the discussion of maternal child health disparities, especially when challenging the current explanations for prevailing disparities in PTB among Black women in the U.S., focused on individual level factors such as such maternal education and utilization of public resources such as WIC and Medi-Cal. In our sample, about half of Black U.S.-born and foreign-born women had more than a high school education, participated in WIC, and utilized Medi-Cal. The state of California is unique in that it

offers multiple options for pregnant persons to obtain health coverage: 1) Presumptive Eligibility for Pregnant Women (immediate and temporary coverage for low-income women who are pregnant and might be eligible for Medi-Cal); 2) Full scope Medi-Cal (coverage for all medically necessary pregnancy-related services, preventive services, and dental services at no cost to eligible women); 3) Pregnancy-related Medi-Cal (coverage for all medically necessary pregnancy-related services for pregnant women who do not qualify for full scope Medi-Cal); 4) Medi-Cal Access Program (MCAP) (low-cost comprehensive coverage for pregnant women with no copayments, deductibles, or coinsurance regardless of citizenship or immigrant status); and 5) Covered California health insurance plans (for those whose household incomes are too high to qualify for Medi-Cal, coverage for comprehensive health care with tax credits to help lower monthly premiums and out-of-pocket costs, with specific citizenship and immigration eligibility requirements). Within the context of the women included in this study, education, insurance, and prenatal utilization did not protect against adverse birth outcomes. Thus, our data emphasize the need for community members, scientists, clinician scientists, policy makers, and private and public funders to prioritize community, state, and federal level interventions to reduce and eliminate structural barriers to advancing health equity such as doula support, group prenatal and pediatric care, paid family leave, affordable child care, affordable and safe housing and neighborhoods, and mental health.

Our data highlight in that even in the presence of presumed social protectors (i.e. health insurance, utilization of public resources, and >12 years education) against adverse outcomes, U.S.-born Black women with diabetes remain at higher risk for PTB and preeclampsia. Although BMI as a predictor and BMI as a modifier with immigrant status

were removed from the final model, obesity increased the risk of PTB among U.S.-born Black women with diabetes. Our data support the need to further evaluate BMI, specifically obesity, as a potential mediator of the relationship between immigrant status and gestational week of delivery among Black women with diabetes and preeclampsia. Although a third of the sample had missing data on BMI, based on preexisting data, we would expect more U.S.-born Black women to be overweight or obese, thus increasing the statistical power to evaluate presence of interactions between immigrant status and obesity. We would also consider assessing for interactions between obesity and preeclampsia, smoking and preeclampsia, and obesity and smoking.

For Black women with diabetes who deliver prior to 37 completed gestational weeks, we did not find an association between immigrant status, gestational age of delivery, and maternal age, in the presence of preeclampsia. For Black women with diabetes and preeclampsia, maternal age appeared not to be a significant predictor of early PTB. Thus, there are appear to be other independent factors contributing to the relationship between immigrant status, preeclampsia, and PTB in Black women with any diabetes who are otherwise insured, educated, and participants in WIC.

Strengths

Although the increased prevalence of preeclampsia in the setting of GDM [124], racial disparities in the prevalence of preeclampsia [125], the interaction between maternal race/ethnicity and chronic hypertension on PTB [126], prevalence of GDM by age group and by race/ethnicity, before and after adjustment for BMI and nativity [127], and PTB as a predictor for subsequent development of Type 2 DM [128] are established patterns, to our knowledge, our study is the first to evaluate the association of immigrant

status, preeclampsia, and gestational age at delivery among an exclusive cohort of Black women with diabetes in California.

The strengths of our study include: 1) the use of population-based sample with a single racial group exclusive to Black women with any diabetes over a total duration of six years; 2) the large number of deliveries by Black women; 3) sufficient statistical power to conduct separate analyses examining the associations between immigrant status, preeclampsia, and other maternal, social, and obstetric factors for PTB and full term births; 4) the use of linked birth certificates and hospital discharge data; 5) the inclusion of youth and young adults aged <20 and 20-29 years, who are usually underrepresented in research; 6) increased representatives of study population and possible generalizability of results to predominantly Black U.S.- and foreign-born populations; 7) presence and categorization of maternal age; 8) evaluation of interactions between immigrant status and key variables, including preeclampsia, smoking, maternal age, BMI; 9) ability to adjust for key variables that are considered shared risk factors for preeclampsia, diabetes, and obesity; and 10) ability to evaluate gestational age at delivery, not just ever PTB.

Limitations

There are several limitations to our study. First, our data provided no delineation between medically indicated and spontaneous preterm births which would have provided more insights into timing and indication for delivery for our study cohort. Second, our data provided no information on the fetal diagnoses or indicators that would lead to recommendations for early delivery by induction or cesarean delivery prior to completion of 39 gestational weeks, particularly given the persistence of prior PTB, UTI, preeclampsia, and smoking. Third, we did not did stratify delivery by the timing of preterm and term

birth (i.e., early preterm, late preterm, early term, and full term). This is analysis we can do in the future. Also, we could not distinguish between spontaneous and iatrogenic (medically indicated) PTB. Previous studies suggest that PTB is better understood and therefore better treated if the causal pathways are categorized in pathways resulting in spontaneous and iatrogenic PTB [129]. From the perspectives of population health management and clinical practice, conducting analyses of spontaneous and indicated PTB are necessary and supported based on significantly large disparities in the prevalence of PTB across racial/ethnic groups as well as the subsequent disparities in perinatal and adult health outcomes [130]. We also do not know how hospital clinicians diagnosed UTI in pregnancy, by urine culture (gold standard) or clinical judgment based on urine analyses and patient symptoms. One explanation for the persistence of UTI as a predictor of PTB could be the presence of proteinuria, signifying possible renal dysfunction from diabetes and hypertensive disorders of pregnancy, including preeclampsia. Our data did not include measures of pregnancy related stress as one of the independent variables that either confounds, mediates, or modifies the relationships between immigrant status and gestational age of delivery among Black women with diabetes, preeclampsia, and obesity. We did not stratify the data by first and second pregnancy to better understand risks, particularly given the increased risk of PTB and preeclampsia among women with a prior history of PTB and preeclampsia. Our future plan is to conduct a secondary analysis that will involve re-categorizing the sample into nulliparous, multiparous with prior PTB, and a referent group of multiparous without prior PTB. Our analysis could not include the specific maternal country of origin and duration of time living in the U.S. relative to the index pregnancy, which would have increased understanding of the role of acculturation in

the relationship between immigrant status, preeclampsia, and obesity among Black women with diabetes. With respect to the differences and similarities in social and health capital between the U.S.-born and foreign-born Black women, we could not collect data on the duration of time in the U.S. prior to birth, specific names of country of birth, patient reported and serum biomarkers of stress, presence and type of medical management of diabetes, and measures of glycemic control. The inclusion of the previous indicators would have allowed us to consider the relationships between acculturation, structural racism, chronic stressors, glycemic control and PTB among U.S. and foreign born Black women.

Implications

Our data demonstrate the need for advanced epidemiological research on the role of preeclampsia, smoking, obesity, and life stressors as mediators of immigrant status and gestational age at delivery among Black women with diabetes. Additionally, studies are needed to further explore the interactions between preeclampsia, smoking, obesity, and life stressors and their effect on delivery outcomes. To do so with accuracy, birth certificate registrars must include accurate information BMI on all certificates. Accuracy and completeness have been shown to be associated with race/ethnicity and preterm birth. One additional analysis could be to calculate the population attributable fraction for PTB among obese Black women with diabetes and preeclampsia to better assess the relative contributions to PTB within this specific community. More so, our data support the need for a longitudinal study that evaluates use of self-reported stress as well as biologic markers of the stress response with the simultaneous examination of maternal, fetal, placental, and newborn outcomes among a diverse and inclusive population of Black women.

Conducting single race/ethnic studies, such as this study, allows for the examination of the presence and magnitude of risk factors for gestational age at delivery beyond race. Such analyses also validate the heterogeneity of Black communities in the U.S. as well as the variety of potentially unidentified or under examined exposures, modifiers, confounders, and mediators, and outcomes. Inclusion of immigrant status in the analysis also contributes to general knowledge of the status and variations in prenatal health and birth outcomes within and among different groups of Blacks in the U.S. population. Such gains in knowledge could lead to new or enhanced customization of surveillance systems and prevention and intervention strategies to mitigate adverse maternal child health outcomes associated with PDGM and GDM among Black women.

Furthermore, if consensus builds among epidemiologists, clinicians, and clinician scientists to view preterm birth as a chronic inflammatory process or vasculature dysfunction in response to chronic life stressors (i.e., structural racism, food apartheid, police brutality, mass incarceration), then we strongly recommend a population based and health systems-based evaluation of the facilitators and barriers to the uptake of pharmacologic interventions such as 17-hydroxyprogesteone (17P, for women with history of recurrent preterm birth) and baby aspirin (for women with a history of early onset preeclampsia and prior preterm birth less than 34 completed gestational weeks), particularly among Black women with any diabetes, aged $\geq$35 years or older, obese, and other significant personal and family history. More importantly, we recommend investment in evidence-based approaches such as doula support and group prenatal and pediatric care throughout pregnancy, birth, and beyond, as a means to mitigate the adverse

impact of structural and life experiences of racism on maternal health, health care experiences, and quality of care.

CONCLUSION

We observed two very striking phenomena in our study cohort of U.S.- and foreign-born Black women. Among a population of Black women with diabetes living in California, where 3 in 4 were educated, enrolled in prenatal care prior to 5 months, and insured, 16% of Black women with singleton pregnancies affected by diabetes gave birth to a premature baby. While more than 40% of foreign-born women were older ($\geq$35 years), and maternal age $\geq$35 was associated with PTB, foreign-born status remains protective. Thus, our data demonstrate the urgent need for advanced epidemiological research to assess the role of preeclampsia, smoking, obesity, stress, and structural racism as potential mediators of the relationship between immigrant status and PTB, and to assess for interactions between preeclampsia and smoking, preeclampsia and obesity, and obesity and smoking.

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