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Authors

Rohlfing, Anne B
Nah, Gregory
Ryckman, Kelli K
et al.

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Maternal cardiovascular disease risk factors as predictors of preterm birth in California: a case–control study

Anne B. Rohlfing ,[1] Gregory Nah,[1] Kelli K. Ryckman,[2] Brittney D. Snyder,[3] Deborah Kasarek,[1] Randi A. Paynter,[4] Sky K. Feuer,[5] Laura Jelliffe-Pawlowski,[1] Nisha I Parikh[6]

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For numbered affiliations see end of article.

Correspondence to
Nisha I Parikh;
nisha.parikh@ucsf.edu

ABSTRACT

Objective To determine whether maternal cardiovascular disease (CVD) risk factors predict preterm birth.

Design Case control.

Setting California hospitals.

Participants 868 mothers with linked demographic information and biospecimens who delivered singleton births from July 2009 to December 2010.

Methods Logistic regression analysis was employed to calculate odds ratios for the associations between maternal CVD risk factors before and during pregnancy (including diabetes, hypertensive disorders and cholesterol levels) and preterm birth outcomes.

Primary outcome Preterm delivery status.

Results Adjusting for the other maternal CVD risk factors of interest, all categories of hypertension led to increased odds of preterm birth, with the strongest magnitude observed in the pre-eclampsia group (adjusted OR (aOR), 13.49; 95% CI 6.01 to 30.27 for preterm birth; aOR, 10.62; 95% CI 4.58 to 24.60 for late preterm birth; aOR, 17.98; 95% CI 7.55 to 42.82 for early preterm birth) and chronic hypertension alone for early preterm birth (aOR, 4.58; 95% CI 1.40 to 15.05). Diabetes (types 1 and 2 and gestational) was also associated with threefold increased risk for preterm birth (aOR, 3.06; 95% CI 1.12 to 8.41). A significant and linear dose response was found between total and low-density lipoprotein (LDL) cholesterol and aORs for late and early preterm birth, with increasing cholesterol values associated with increased risk (likelihood χ^2 differences of 8.422 and 8.019 for total cholesterol for late and early, and 9.169 and 10.896 for LDL for late and early, respectively). Receiver operating characteristic curves using these risk factors to predict late and early preterm birth produced C statistics of 0.601 and 0.686.

Conclusion Traditional CVD risk factors are significantly associated with an increased risk of preterm birth; these findings reinforce the clinical importance of integrating obstetric and cardiovascular risk assessment across the healthcare continuum in women.

Strengths and limitations of this study

- ► Directly measured serum biomarkers as well as demographic data were linked in our population sample.
- ► Our cohort was strengthened by a high proportion of early preterm births.
- ► The population was limited in size therefore diversity, representing only one geographic location.

INTRODUCTION

Preterm birth is an ongoing health crisis both nationally and globally, occurring at a rate of 9.85% in the USA in 2016, an increase for the first time in decades for the last 2 years.[1] Defined as delivery at <37 weeks of gestational age, preterm birth occurs spontaneously (without obvious medical reason) in roughly two-thirds of cases in the USA and is medically indicated in the remaining one-third.[2] Preterm birth is linked to a wide range of adverse health outcomes for both mothers and infants. Infants born prematurely are more likely to suffer from respiratory distress syndrome, sepsis, intraventricular haemorrhage and necrotising enterocolitis shortly after birth, and stay in the hospital an average of 12 days longer than full term births.[2] They are also more likely to have long-term complications such as cerebral palsy and retinopathy, as well as increased incidence of chronic diseases such as hypertension, cardiovascular disease (CVD) and type 2 diabetes mellitus.[2 3] Mothers who give birth prematurely have higher rates of CVD-related hospitalisations directly related to the number of preterm births (spontaneous or medically indicated) and more recent data have emerged that continue to demonstrate preterm birth predicts not only increased risk of future CVD, death from CVD and stroke but also development of chronic hypertension, type 2 diabetes mellitus and hyperlipidaemia.[4–8]

There are multiple risk factors for preterm birth, including but not limited to race/ethnicity, maternal age, socioeconomic status, substance use, use of assisted reproductive

technology, parity, maternal infections, maternal height and weight, maternal stress and depression, cervical length, history of preterm birth, fetal fibronectin levels, placenta previa, premature rupture of membranes, fetal sex and fetal growth restriction.[2 9] Traditional CVD risk factors such as hypertension and diabetes prior to pregnancy, elevated cholesterol and triglycerides, smoking and obesity have all been shown to be associated with preterm birth, although the magnitude of their effects as well as their interactions with race/ethnicity have shown notable variation in the current literature (table 1).[10–25]

In this study, we (1) sought to identify women at high risk of preterm birth based on readily ascertained CVD risk markers including early pregnancy lipids, hypertension (inclusive of both prior hypertension and the development of hypertension during pregnancy), smoking and diabetes (inclusive of both prior diabetes history and gestational diabetes). Given the association between preterm birth and later CVD risk in women, we (2) sought to better understand the contribution of these risk factors to early (<32 weeks) and late preterm birth (32–36 weeks). The availability of directly measured fasting lipids with linked clinical information on hypertension and diabetes in a well-characterised case–control study of preterm birth in 1000 women allowed us to carry out these two major study aims.[25]

MATERIALS AND METHODS

Study population

Patients were selected from a California-based cohort of 1 004 039 singleton births from July 2009 to December 2010, narrowed to 61 339 births for whom there was demographic information recorded by the California Office of Statewide Health Planning and Development (OSHPD) in birth certificates and discharge records, as well as first trimester (weeks 10–13) serum samples stored by the California Biobank Program. From this group, 1000 subjects were selected randomly and divided evenly between full term and preterm births, but with fortification for early preterm birth (20–31 weeks) as described previously.[25 26] Only women with complete data and biospecimen measurements were included in the final group (n=868), which consisted of 457 term (37 weeks or more), 249 late preterm (32–36 weeks) and 162 early preterm (<32 weeks), for whom serum data from early pregnancy was available and linked to demographic information.

Ascertainment of CVD risk factors prior to and during pregnancy

In addition to self-reported information of race/ethnicity and smoking status during pregnancy on birth certificates, ICD-9 codes (online supplementary appendix 1) from hospital discharge records were used to identify patients with diabetes (types 1 and 2 as well as gestational) and hypertension, which was further subdivided into the categories of chronic hypertension, gestational hypertension and pre-eclampsia de novo or imposed on prior hypertension. Obesity was measured as body mass index (BMI) in kg/m^2 at onset of pregnancy with cutpoints of <18.5 for underweight, 18.5–24.9 for normal, 25–29.9 for overweight and ≥30 for obese. Serum samples from the California Biobank were collected at 15 to 20 weeks gestation during pregnancy, separated and stored at −80 degrees, then aliquoted and tested with enzymatic colorimetric tests on a Roche Cobas c111 instrument to measure total cholesterol (mg/dL), LDL (mg/dL), high-density lipoprotein (HDL) (mg/dL) and triglycerides (mg/dL).

Patient and public involvement

There was no patient or public involvement in the use of the cohort for this study.

Data availability

Our data is gathered from the California OSHPD for demographics with correlated serum sample results collected from the California Biobank Program; the deidentified data can be made available by contacting PretermBirth@ucsf.edu, with reuse permitted on case by case basis per the Initiative's agreement. No additional data available.

Statistical methods

Descriptive statistics, including percentages and means with SD, were obtained for the population using gestational age categories of full term, all preterm, and late and early preterm categories. Logistic regression analysis in unadjusted and multivariable-adjusted models was used to assess the association between maternal CVD risk factors and preterm birth, both late preterm and early preterm (referent=full term). Maternal CVD risk factors studied included the following: age, race/ethnicity (black, Hispanic, Asian or other compared with white), smoking during pregnancy (yes/no), diabetes (included both type 1 and type 2 and gestational diabetes vs none), hypertension (chronic hypertension, gestational hypertension or pre-eclampsia, vs none), total cholesterol, LDL, HDL and triglycerides (considered in quartiles, with first quartile=referent, online supplementary appendix 2). The multivariable model was adjusted for all of these risk factors. Statistical significance was determined for adjusted ORs (aORs) with 95% CIs, with a two-tailed p value <0.05. Tests for linear trend for cholesterol was performed for continuous and quartile unadjusted models. In order to determine the ability of statistically significant multivariable-adjusted CVD risk factors to discriminate between preterm birth and full term outcomes, we constructed receiver operating characteristic (ROC) curves for all births. Statistical Analysis Software (SAS V.9.4) was employed for all statistical analysis.

RESULTS

Study population

Among the study population of 868 women, there were 249 late preterm births (32–36 weeks) and 162 early preterm (20–31 weeks) for a total of 411 preterm births total. Of

Table 1 Maternal CVD risk factors and established relationships with preterm birth

Risk factor	Reference	Sample size: Total #	Sample size: Preterm # (definition)	Adjusted OR or risk ratio (95% CI)
Age	Cnattingius *et al*[10]	499 947	29 937 (<36 weeks)	**OR 2.1 (1.9 to 2.2)** for age >/=35 years in nulliparous non-smokers compared with multiparous non-smokers age 20 to 24 years **OR 2.3 (2.1 to 2.5)** for age >/=35 years in nulliparous smokers compared with multiparous nonsmokers age 20 to 24 years
	Meis *et al*[11]	2929	120 (medically indicated <37 weeks)	**OR 2.42 (1.57 to 3.74)** for age >30 years compared with age </=30 years
	Premkumar *et al*[12]	23 425	2069 (<37 weeks)	**OR 1.29 (1.08 to 1.54)** for age <25 years compared with age 30 to 34 years **OR 1.27 (1.05 to 1.55)** for age >40 years compared with age 30 to 34 years
Race/ethnicity	Harlow *et al*[13]	14 948	448 (spontaneous <37 weeks)	**OR 2.0 (1.4 to 2.9)** for black race compared with white
	Meis *et al*[11]	2929	120 (medically indicated <37 weeks)	**OR 1.56 (1.02 to 2.40)** for black ethnicity compared with white
	Kistka *et al*[14]	711 015	14 611 (<37 weeks)	**OR 2.21 (2.11 to 2.31)** for black race compared with white
	Premkumar *et al*[12]	23 425	2069 (<37 weeks)	OR 1.08 (0.89 to 1.30) for African-American compared with white OR 1.04 (0.88 to 1.22) for Latina/Hispanic compared with white OR 0.91 (0.79 to 1.05) for Asian/Pacific Islander compared with white
Smoking	Harlow *et al*[13]	14 948	124 (medically indicated <37 weeks)	OR 1.1 (1.0 to 1.2) for smoking >5 cigarettes/day compared with no smoking
	Bhattacharya *et al*[15]	7090	318 (<37 weeks)	**OR 1.47 (1.27 to 1.71)** for smoking >10 cigarettes/day compared with no smoking
	Premkumar *et al*[12]	23 425	2069 (<37 weeks)	OR 1.34 (0.99 to 1.80) for smoking compared with no smoking
Hypertension	Meis *et al*[11]	2929	120 (medically indicated <37 weeks)	**OR 4.06 (2.29 to 7.22)** for chronic hypertension compared with none
	Sibai *et al*[16]	3499	632 (<37 weeks)	**OR 2.4 (2.1 to 2.7)** for chronic hypertension compared with none
	Premkumar *et al*[12]	23 425	2069 (<37 weeks)	**OR 2.74 (2.28 to 3.29)** for chronic hypertension compared with none

Continued

Table 1 Continued

Risk factor	Reference	Sample size: Total #	Sample size: Preterm # (definition)	Adjusted OR or risk ratio (95% CI)
Diabetes	Harlow *et al*[13]	14 948	124 (medically indicated <37 weeks), 448 (spontaneous <37 weeks)	**OR 1.4 (1.1 to 1.8)** for abnormal glucose tolerance testing in spontaneous preterm births compared with none **OR 2.2 (1.2 to 4.1)** for abnormal glucose tolerance testing in medically indicated preterm births compared with none
	Sibai *et al*[16]	3199	555 (<37 weeks)	**OR 2.7 (2.3 to 3.2)** for pregestational insulin-dependent diabetes compared with none
	Hedderson *et al*[17]	46 230	1956 (spontaneous <37 weeks)	**RR 1.23 (1.08 to 1.41)** for abnormal glucose tolerance testing compared with none **RR 1.42 (1.15 to 1.77)** for gestational diabetes compared with none
	Premkumar *et al*[12]	23 425	2069 (<37 weeks)	**OR 2.75 (2.18 to 3.47)** for pregestational diabetes compared with none
Obesity	Hendler *et al*[18]	2910	296 (spontaneous <37 weeks)	**OR 0.57 (0.39 to 0.83)** for obese (BMI>/=30 kg/m^2) compared with non-obese (BMI <30 kg/m^2)
	McDonald *et al*[19]	~1 095 834	None given (but defined as <37 weeks)	**RR 1.24 (1.13 to 1.37)** for overweight and obese compared with normal (BMI at least <24 kg/m^2 for all included studies, with range given meta-analysis)
	Cnattingius *et al*[20]	1 599 551	67 059 (32–36 weeks)	**OR 1.22 (1.18 to 1.27)** for BMI 25 to 29.9 kg/m^2, medically indicated OR 0.98 (0.96 to 1.01) for BMI 25 to 29.9 kg/m^2, spontaneous **OR 1.62 (1.54 to 1.71)** for BMI 30 to 34.9 kg/m^2, medically indicated OR 1.01 (0.98 to 1.05) for BMI 30 to 34.9 kg/m^2, spontaneous **OR 2.00 (1.84 to 2.18)** for BMI 35 to 39.9 kg/m^2, medically indicated OR 1.06 (1.00 to 1.13) for BMI 35 to 39.9 kg/m^2, spontaneous **OR 2.45 (2.15 to 2.79)** for BMI >40 kg/m^2, medically indicated OR 1.13 (0.95 to 1.33) for BMI >40 kg/m^2, spontaneous With all groups compared with normal (BMI 18.5 to <25 kg/m^2)
	Premkumar *et al*[12]	23 425	2069 (<37 weeks)	OR 1.03 (0.91 to 1.17) for overweight (BMI 25 to 29.9 kg/m^2) compared with normal (BMI 18 to 24.9 kg/m^2) **OR 1.21 (1.04 to 1.40)** for obese (BMI >30 kg/m^2) compared with normal (BMI 18 to 24.9 kg/m^2)

Continued

Table 1 Continued

Risk factor	Reference	Sample size: Total #	Sample size: Preterm # (definition)	Adjusted OR or risk ratio (95% CI)
Hyperlipidaemia	Chatzi *et al*[21]	625	74 (<37 weeks)	RR 1.13 (0.91 to 1.40) for triglycerides per increase in 50 mg/dL
				RR 1.08 (0.88 to 1.33) for HDL per increase in 15 mg/dL
				RR1.17 (0.77 to 1.1.78) for LDL cholesterol per increase in 30 mg/dL
				RR 1.24 (0.99 to 1.56) for total cholesterol increase in 40 mg/dL
	Catov *et al*[22]	938	146 (34–37 weeks)	OR 1.38 (0.80 to 2.36) for fourth quartile total cholesterol (196 to 318 mg/dL) compared with second quartile (156–172)
				OR 1.86 (1.10 to 3.15) for first quartile total cholesterol (94 to 155 mg/dL) compared with second quartile (156–172)
				OR 1.07 (0.63 to 1.83) for fourth quartile LDL (124 to 233 mg/dL) compared with second quartile (89–104)
				OR 1.60 (0.96 to 2.68) for first quartile LDL (26 to 88 mg/dL) compared with second quartile (89–104)
				OR 0.99 (0.58 to 1.67) for fourth quartile triglycerides (78 to 318 mg/dL) compared with second quartile (44–57)
				OR 1.13 (0.68 to 1.88) for first quartile triglycerides (16 to 43 mg/dL) compared with second quartile (44–57)
				OR 1.52 (0.92 to 2.49) for fourth quartile HDL (64 to 118 mg/dL) compared with second quartile (47–54)
				OR 1.05 (0.62 to 1.79) for first quartile HDL (25 to 46 mg/dL) compared with second quartile (47–54)
	Harville *et al*[23]	1142	67 (<37 weeks)	RR 1.11 (0.84 to 1.46) for total cholesterol as continuous variable
				RR 0.92 (0.73 to 1.17) for HDL as continuous variable
				RR 1.13 (0.86 to 1.48) for LDL as continuous variable
				RR 1.10 (0.84 to 1.42) for triglycerides as continuous variable
	Magnussen *et al*[24]	4990	272 (<37 weeks)	OR 1.3 (0.9 to 2.0) for fifth quintile total cholesterol (5.7 to 9.9 mmol/L) compared with first quintile (2.1 to 4.1 mmol/L)
				OR 1.4 (0.9 to 2.2) for first quintile HDL (1.9 to 3.1 mmol/L) compared with first quintile (0.6 to 1.2 mmol/L)
				OR 1.3 (0.8 to 2.2) for fifth quintile triglycerides (1.6 to 9.6 mmol/L) compared with first quintile (0.2 to 0.6 mmol/L)
	Alleman 2013[40]	2699	200 (<37 weeks)	OR 1.03 (0.89 to 1.19) for total cholesterol as continuous variable
				OR 1.01 (0.88 to 1.17) for LDL as continuous variable
				OR 0.96 (0.83 to 1.11) for HDL as continuous variable
				OR 1.02 (0.88 to 1.17) for triglycerides as continuous variable

ORs or RRs with p<0.05 are highlighted in bold.
BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2 Maternal characteristics by gestational age among singleton births in California

Variable	Full term (≥37 weeks, n=457)	All preterm (<37 weeks, n=411)	Late preterm (32–36 weeks, n=249)	Early preterm (20–31 weeks, n=162)
Maternal age, mean (SD) in years	29.9 (6.0)	29.5 (6.2)	29.6 (6.2)	29.4 (6.4)
Race/ethnicity, n (%)				
White	157 (34)	140 (34)	86 (34)	54 (33)
Black	6 (1)	10 (2)	5 (2)	5 (3)
Hispanic	205 (45)	176 (43)	109 (44)	67 (41)
Asian	69 (15)	61 (15)	40 (16)	21 (13)
Other	20 (4)	24 (6)	9 (4)	15 (9)
Smoking status, n (%)				
No	450 (98)	400 (97)	245 (98)	155 (96)
Yes	7 (2)	11 (3)	4 (2)	7 (4)
Hypertension, n (%)				
None	437 (96)	323 (79)	204 (82)	119 (73)
Chronic hypertension	6 (1)	12 (3)	3 (1)	9 (6)
Gestational hypertension	7 (2)	9 (2)	7 (3)	2 (1)
Pre-eclampsia	7 (2)	67 (16)	35 (14)	32 (20)
Diabetes, n (%)				
No	451 (99)	392 (95)	238 (96)	154 (95)
Yes	6 (1)	19 (5)	11 (4)	8 (5)
Weight by BMI in kg/m^2, n (%)				
Underweight (<18.5)	26 (6)	20 (5)	9 (4)	11 (7)
Normal (18.5–24.9)	250 (55)	213 (52)	138 (55)	75 (46)
Overweight (25–29.9)	107 (23)	90 (22)	49 (20)	41 (25)
Obese (≥30)	74 (16)	88 (21)	53 (60)	35 (22)
Cholesterol, mean (SD) in mg/dL				
Total	224 (39)	228 (41)	227 (38)	230 (45)
LDL	116 (34)	111 (34)	109 (32)	113 (37)
HDL	73 (17)	76 (17)	76 (17)	76 (17)
Triglycerides	202 (67)	204 (77)	204 (77)	205 (76)

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

all the preterm births, only nine were medically indicated (2%) compared with spontaneous; three preterm births were from nulliparous women (0.7%) compared with 0.4% of full term. The distribution of age and race among all gestational ages was similar, with average maternal age at birth ranging from 29.5 years for preterm births to 29.9 years for full term births and the majority of births by white and Hispanic mothers (table 2). This distribution for race and age was also consistent for both late and early preterm births (average age of 29.6 vs 29.4 years, 34% vs 33% white, and 44% vs 41% Hispanic). The overall population had a low prevalence of smoking at 2% for full term and 3% for preterm. There were more normal weight and overweight women with full term births and more obese women with preterm births. There was a higher prevalence of diabetes in preterm births, both late and early, at 5% compared with 1% of full term births. The diagnosis of pre-eclampsia was also more prevalent in preterm versus full term births, occurring among 16% vs 2%, respectively; mothers with early preterm births had the highest proportion at 20%, in addition to the highest proportion of chronic hypertension alone at 6%. Mean cholesterol values, including total, LDL, HDL and triglycerides, were comparably dispersed among all gestational age groups.

CVD risk factor associations

The association between maternal CVD risk factors and preterm birth was assessed in multivariable logistic regression models (table 3). Neither maternal age nor race/ethnicity was found to be significant predictors of preterm birth, after adjusting for all other risk factors. Smoking status was positively associated only with early preterm birth (aOR, 3.60; 95% CI 1.14 to 11.41). All hypertensive categories led to increased odds of preterm birth, with significant associations of pre-eclampsia across all preterm gestational age categories (aOR, 13.49; 95% CI 6.01 to 30.27 for all preterm; aOR, 10.62; 95% CI 4.58 to 24.60 for late preterm; aOR, 17.98; 95% CI 7.55

Table 3 Adjusted ORs for maternal CVD risk factors before and during pregnancy

Variable	Adjusted ORs (95% CI)		
	All preterm (<37 weeks, n=411)	Late preterm (32–36 weeks, n=249)	Early preterm (20–31 weeks, n=162)
Maternal age	0.99 (0.97 to 1.02)	0.99 (0.96 to 1.02)	0.99 (0.95 to 1.02)
Hypertension			
Chronic hypertension	2.23 (0.75 to 6.64)	1.01 (0.24 to 4.30)	4.58 (1.40 to 15.05)*
Gestational hypertension	1.95 (0.64 to 4.99)	2.20 (0.73 to 6.62)	1.08 (0.21 to 5.49)
Pre-eclampsia	13.49 (6.01 to 30.27)*	10.62 (4.58 to 24.60)*	17.98 (7.55 to 42.82)*
Diabetes	3.06 (1.12 to 8.41)*	3.42 (1.17 to 9.95)*	2.44 (0.74 to 8.10)
Race/ethnicity			
White	–	–	–
Hispanic	0.92 (0.65 to 1.30)	0.95 (0.65 to 1.39)	0.90 (0.56 to 1.43)
Black	1.45 (0.48 to 4.38)	1.50 (0.43 to 5.29)	1.58 (0.41 to 6.06)
Asian	1.14 (0.74 to 1.77)	1.21 (0.74 to 1.97)	1.09 (0.59 to 2.01)
Other	1.26 (0.63 to 2.51)	0.81 (0.34 to 1.92)	2.22 (0.99 to 4.99)
Smoking status	2.02 (0.73 to 5.58)	1.29 (0.36 to 4.58)	3.60 (1.14 to 11.41)*
Total cholesterol, mg/dL			
1st quartile	–	–	–
2nd quartile	1.68 (0.98 to 2.89)	1.79 (0.96 to 3.34)**	1.64 (0.81 to 3.32)**
3rd quartile	1.69 (0.85 to 3.34)	2.23 (1.02 to 4.84)**	1.05 (0.41 to 2.67)**
4th quartile	1.95 (0.78 to 4.88)	2.32 (0.81 to 6.63)**	1.60 (0.46 to 5.49)**
HDL, mg/dL			
1st quartile	–	–	–
2nd quartile	1.04 (0.63 to 1.71)	1.28 (0.69 to 2.38)	0.60 (0.29 to 1.22)
3rd quartile	1.15 (0.63 to 2.10)	1.12 (0.50 to 2.48)	1.09 (0.46 to 2.55)
4th quartile	0.90 (0.42 to 1.95)	0.91 (0.32 to 2.63)	0.81 (0.26 to 2.49)
LDL, mg/dL			
1st quartile	–	–	–
2nd quartile	0.86 (0.53 to 1.39)	0.99 (0.59 to 1.66)**	1.15 (0.64 to 1.07)**
3rd quartile	0.55 (0.30 to 1.01)	0.87 (0.46 to 1.64)**	0.46 (0.21 to 1.01)**
4th quartile	0.78 (0.34 to 1.77)	1.01 (0.39 to 2.64)**	1.14 (0.39 to 3.33)**
Triglycerides, mg/dL			
1st quartile	–	–	–
2nd quartile	0.73 (0.48 to 1.11)	0.87 (0.55 to 1.39)	0.53 (0.30 to 0.95)
3rd quartile	0.78 (0.50 to 1.20)	0.83 (0.51 to 1.37)	0.68 (0.38 to 1.23)
4th quartile	1.03 (0.62 to 1.70)	1.00 (0.56 to 1.80)	1.07 (0.55 to 2.06)

** P<0.05 for trend. aORs adjusted for all co-variables listed in Table 2.
*Statistically significant at 95% confidence level
CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

to 42.82 for early preterm) and between women with chronic hypertension alone for early preterm birth (aOR, 4.58; 95% CI 1.40 to 15.05). Similarly, the presence of either chronic or gestational diabetes was associated with increased odds of preterm birth (aOR, 3.06; 95% CI 1.12 to 8.41). On further evaluating diabetes with late and with early preterm subcategories, only late preterm was significant (aOR, 3.42; 95% CI 1.17 to 9.95 for late preterm, aOR, 2.44; 95% CI 0.74 to 8.10 for early preterm birth). In quartile-based analysis, total cholesterol in the third quartile versus first was significantly associated with late preterm birth (aOR, 2.23; 95% CI 1.02 to 4.84) (table 3). A statistically significant linear dose response across quartiles was found for total and LDL cholesterol for both late and early preterm birth (p values of 0.01 and 0.02 for total for late and early, respectively, and p values of 0.01 and 0.004 for LDL for late and early, respectively).

Model discrimination by gestational age

An ROC curve was constructed for any preterm birth (<37 weeks) based on the multivariable CVD risk factors noted above, yielding a C statistic of 0.625. Additional

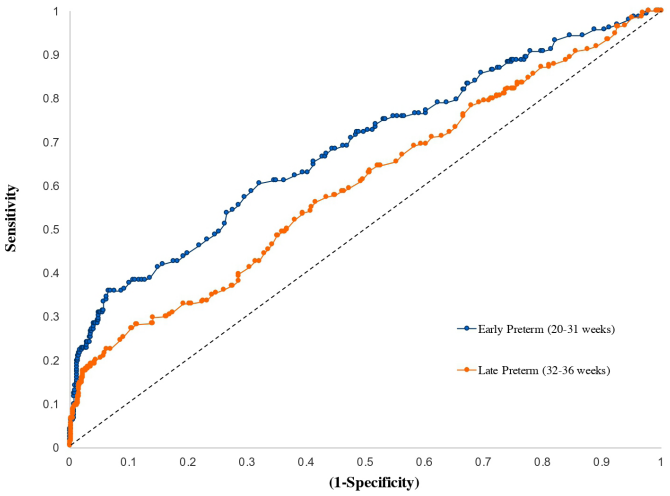

Figure 1 ROC curve for late and early preterm birth. ROC curves based on significant multivariate models of cardiovascular disease risk for late and early preterm birth, with C statistics of 0.601 and 0.686, respectively. ROC, receiver operating characteristic.

ROC curves were constructed for late and early preterm birth, yielding C statistics of 0.601 and 0.686, respectively (figure 1).

DISCUSSION

In this case–control study of prenatal maternal CVD risk factors as predictors of preterm birth among 868 women in California, we found that (1) hypertension and diabetes were significantly associated with preterm birth, (2) hypertension was more strongly associated with early preterm birth, (3) diabetes was more strongly associated with late preterm birth and (4) higher total and LDL cholesterol values were associated with up to twofold increased odds of preterm birth. Our final model yielded modest C statistics of 0.601 for late preterm birth and 0.686 for early preterm birth. These findings suggest that using CVD risk factors, which are both familiar and easily accessible to clinicians, and available at a relatively low cost, could be useful for identifying some women at increased odds of preterm birth both before and during pregnancy.

Age

While age is one of the most well-established risk factors for CVD, the effects of maternal age on preterm birth are not as clear. Models have described increased risk of spontaneous preterm birth among younger mothers and increased risk of medically induced preterm birth among older mothers (table 1), although recent literature suggests that even with adjustment for confounders, advanced maternal age (ie, >40 years) is associated with spontaneous preterm birth risk.[27] Our results did not show a significant risk when using age as a continuous variable for any preterm, late preterm or early preterm birth. It should be noted however that our population-based was primarily centred around patients aged 29–30 years.

Race/ethnicity

Similar to the distribution of CVD, preterm birth unequally affects women based on race and ethnicity.[2] While the cause of this disparity remains unknown, similar hypotheses to CVD risk regarding access to care and chronic stress have been postulated.[28 29] Whereas previous studies have demonstrated significant risk associated with black/African–American patients, our study did not find significance, which is likely due to the loss of power from our study population's unique demographics, of which only 10 women in the preterm birth group were black with a majority being Hispanic.

Smoking

Cigarette smoking is proposed to predispose to preterm birth both by carbon monoxide-induced fetal hypoxia and by nicotine-induced vasoconstriction and carries a similar dose response effect as seen on cigarette smoke and CVD risk.[30] We showed a significant association between smoking during pregnancy and risk of early preterm birth, although the threefold risk increase is higher than the almost twofold increase reported most often in prior studies. In our study, only 11 women in the entire preterm population reported smoking during pregnancy, representing 3% of the preterm group compared with the national average among pregnant women of 7.2%.[31] This difference in self report is likely the reason that the estimates were not significant at a 95% confidence level, although they shared similar odds to previous work.

Hypertension

The spectrum of hypertensive diseases during pregnancy ranges from chronic hypertension (prior to pregnancy or diagnosed within the first 20 weeks), gestational hypertension (developing after 20 weeks), to pre-eclampsia (its own disease of marked hypertension and proteinuria). While the mechanism of pre-eclampsia is thought most likely to be immunologic, chronic hypertension itself is a risk factor to developing the disease and chronic vasoconstriction is thought to be part of the preterm birth risk pathophysiology for both pre-eclampsia and the other hypertensive disorders.[32] The odds for hypertensive diseases in pregnancy were of similar magnitude in our study compared with previously published data for chronic and gestational hypertension (table 1), but notably our most significant and highest odds were seen for pre-eclampsia, with a risk increase of 10-fold to 17-fold. Although our population included a relatively high number of patients with pre-eclampsia that might have increased these ratios, the overall trend for hypertension, especially with high risk for early preterm births, highlights the important role in the development of this complication.

Diabetes

Specific mechanisms by which diabetes leads to increased risk of preterm birth are not fully known; however, some studies have suggested links to endothelial dysfunction and oxidative stress that inhibit uterine relaxation, both mechanisms that are also necessary in the development of atherosclerosis and CVD risk in adults.[33 34] Even abnormal glucose tolerance testing without the diagnosis of diabetes has been shown to be associated with preterm birth risk (table 1), and in our study, we found similarly that diabetes was associated with a twofold to threefold risk of preterm birth.

Cholesterol

The association between cholesterol levels and preterm birth risk has shown varying results, most of which have proven non-significant and show trends toward increasing risk with either low cholesterol and triglyceride levels or high cholesterol and triglyceride levels (table 1). Hypotheses for these differences include that lower values of cholesterol, and in particular triglycerides, are associated with poor nutritional status, a confounding risk factor for preterm birth, while elevated levels suggest a proatherogenic pathophysiology.[22 24] In our study, similar to others, we tested cholesterol and triglyceride levels by quartile rather than as continuous variables to try to differentiate these trends. While no particular quartile showed a significant increase in odds, the overall trend in increasing total cholesterol and LDL was associated with increasing odds. The overall averages for our patients of LDL and total cholesterol values are above the accepted goal values for high CVD risk in older individuals, making this trend clinically significant as well.

Integrating obstetric and CVD preventive care

Integration of obstetrics and later primary care and cardiovascular prevention has been recently endorsed by national and international physician societies.[35 36] The peripartum period is an ideal window of opportunity to identify and intervene on at risk women. With over 4 million women giving birth in the USA each year, and with ~85% of women undergoing a pregnancy during her lifetime, the peripartum period represents a window of healthcare opportunity for the majority of women in the USA. For instance, over 91% of women use healthcare in the late postpartum period—2 months to 2 years postpartum.[37] Therefore, identifying and preventing chronic diseases prepregnancy, at delivery and postpartum would be highly impactful. Within the context of our study findings, early recognition of CVD risk factors in women may help identify women at risk for preterm birth and for later CVD. Aggressive modification of risk factors prepregnancy and interpregnancy is likely warranted and may prevent preterm birth in both an index and subsequent pregnancies.

Strengths and limitations

This study represents a unique patient population that has both linked maternal serum and demographic data, strengthened by the high proportion of early preterm births. Our study was limited by its smaller sample size and a certain degree of selection bias. Because the sample was drawn randomly from all women participating in first and second trimester prenatal screening in the state of California, and who had an ultrasound dating prior to 20 weeks, this bias is particularly of concern to women who do not participate in prenatal screening or enter care after the first trimester. This is most notably seen in effects on race/ethnicity and smoking status. Subsequent studies will benefit from more focused testing of associations in group not well represented in this sample including black women. Given its single geographic focus in the state of California, broader generalisation of the results is also limited. We chose not to include BMI in our final model, given the variability in the protective or negative effects of obesity on preterm birth risk, as well as its lack of use in most recent Pooled Cohorts ASCVD Risk Score model.[38 39] In addition, while much of the literature has separated out spontaneous and medically indicated preterm births as clinically and phenotypically separate outcomes, we were unable to differentiate between the two groups in this study due to sample size limitations.

CONCLUSIONS

The results of this study highlight how hypertension and diabetes, as well as total cholesterol and LDL cholesterol values, are associated with increased risk of preterm birth, particularly early preterm birth, suggesting a potential proartherogenic profile that starts before and during pregnancy and continues postpartum with mothers developing further CVD progression. Further refinement of hypertension categories and the use of a broader validation population along with analyses focused on assessing patterns in early term births (37 and 38 weeks) could be used to further refine a scoring model similar to the original Framingham model and current ASCVD pooled cohort equation to help clinicians more easily identify women at increased risk for preterm birth using CVD risk factors. The significant associations found between hypertension and diabetes to preterm birth risk most importantly reinforce the ongoing clinical need to integrate obstetric and cardiovascular risk assessment across the healthcare continuum in women.

Author affiliations
[1]Division of Cardiology, Department of Medicine, University of California San Francisco, San Francisco, California, USA
[2]Epidemiology, University of Iowa, Iowa City, Iowa, USA
[3]Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA
[4]Preterm Birth Initiative, University of California San Francisco, San Francisco, California, USA
[5]Obstetrics and Gynecology, University of California San Francisco, San Francisco, California, USA
[6]Cardiology, University of California San Francisco, San Francisco, California, USA

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Data availability statement Data are available upon reasonable request. Our data is gathered from the California Office of Statewide Health Planning and Development (OSHPD) for demographics with correlated serum sample results collected from the California Biobank Program; the deidentified data can be made available by contacting PretermBirth@ucsf.edu, with reuse permitted on case by case basis per the Initiative's agreement. No additional data available.

ORCID iD

Anne B. Rohlfing http://orcid.org/0000-0001-9784-4223

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