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Pre-pregnancy or first-trimester risk scoring to identify women at high risk of preterm birth

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Abstract

Objective To develop a pre-pregnancy or first-trimester risk score to identify women at high risk of preterm birth.

Study design In this retrospective cohort analysis, the sample was drawn from California singleton livebirths from 2007 to 2012 with linked birth certificate and hospital discharge records. The dataset was

divided into a training (2/3 of sample) and a testing (1/3 of sample) set for discovery and validation. Predictiv

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Appendix A
Table A1

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejogrb.2018.11.004>.

e models for preterm birth using pre-pregnancy or first-trimester maternal factors were developed using backward stepwise logistic regression on a training dataset. A risk score for preterm birth was created for each pregnancy using beta-coefficients for each maternal factor remaining in the final multivariable model. Risk score utility was replicated in a testing dataset and by race/ethnicity and payer for prenatal care.

Results The sample included 2,339,696 pregnancies divided into training and testing datasets. Twenty-three maternal risk factors were identified including several that were associated with a two or more increased odds of preterm birth (preexisting diabetes, preexisting hypertension, sickle cell anemia, and previous preterm birth). Approximately 40% of women with a risk score ≥ 3.0 in the training and testing samples delivered preterm (40.6% and 40.8%, respectively) compared to 3.1–3.3% of women with a risk score of 0.0 [odds ratio (OR) 13.0, 95% confidence interval (CI) 10.7–15.8, training; OR 12.2, 95% CI 9.4–15.9, testing). Additionally, over 18% of women with a risk score ≥ 3.0 had an adverse outcome other than preterm birth.

Conclusion Maternal factors that are identifiable prior to pregnancy or during the first-trimester can be used to create a cumulative risk score to identify women at the lowest and highest risk for preterm birth regardless of race/ethnicity or socioeconomic status. Further, we found that this cumulative risk score could also identify women at risk for other adverse outcomes who did not have a preterm birth. The risk score is not an effective screening test, but does identify women at very high risk of a preterm birth.

Keywords

Cumulative risk; First-trimester; Preterm birth; Risk score; Beta-coefficient

Introduction

After several years of decline, rates of preterm birth (<37 weeks gestation) in the United States increased in 2015 and 2016 [1,2]. Identifying women at elevated risk for preterm birth early in pregnancy allows for increased monitoring, consideration of potentially therapeutic interventions, and planning for the possibility of a preterm infant [3–6]. While preterm birth prediction models have been developed using maternal characteristics and biomarkers [7–15], no cumulative risk scoring tools currently exist.

Some clinical specialties have routinely used cumulative risk scores to predict disease [16–18]. These scores take into account the magnitude of risk associated with each factor to create a personalized cumulative risk score. A common methodology for risk score creation is to sum regression coefficients calculated from multivariable modeling [16,18]. Such a method may be useful for preterm birth given its multifactorial nature and the existence of current and emerging therapies [3–5,7–14].

Here, we developed and tested a pre-pregnancy or first-trimester cumulative risk scoring tool for preterm birth using beta-coefficients from multivariable models. Because preterm birth shares risk factors for other adverse maternal and infant outcomes [19–23], we also evaluated whether scores identified women with adverse outcomes who did not have preterm

birth. Given racial and economic disparities in preterm birth, risk scores were evaluated overall and by racial/ethnic and payer subgroups [24,25].

Methods

In this retrospective cohort study, our sample was drawn from California live births between January 1, 2007 - December 31, 2012 (n = 3,160,268). The sample was restricted to singleton births with gestations 22–42 weeks in a birth cohort database maintained by the California Office of Statewide Health Planning and Development (n = 2,889,487). This database contains linked birth and death certificates, as well as detailed information on maternal and infant characteristics and hospital discharge diagnoses and procedures recorded as early as one year before delivery and as late as one year post-delivery. Data files provided diagnoses and procedure codes based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) [26]. Gestation at birth was obtained from birth certificate by best obstetric estimate of gestation. To restrict our sample to plausible gestational age and birthweight combinations, infants with a birthweight outside of three standard deviations from the mean by sex were removed (n = 2,869,415) [27]. The sample was further restricted to mothers who presented for prenatal care in the first-trimester (n = 2,339,696). The study population was randomly divided into training and testing samples at a 2:1 ratio (n = 1,559,797 and n = 779,899 respectively) (Supplemental Fig. S1).

Clinical characteristics of women who delivered <37 weeks gestation were compared to those of women who delivered between 37 and 42 completed weeks gestation in the training dataset, using logistic regression to calculate univariable odds ratios (OR) and 95% confidence intervals (95% CI). Comparisons of maternal factors using data from birth certificate records included: Black, Hispanic, Asian, or “other” versus White non-Hispanic race/ethnicity; age <18 years or >34 years versus maternal age 18 to 34 years at delivery; education <12 years or >12 years versus 12 years; nulliparous versus multiparous; public insurance for prenatal care (Medi-Cal, health coverage for low-income persons) versus not; maternal birthplace outside of the United States versus within the United States; report of smoking during pregnancy versus no report of smoking; and BMI (calculated from pre-pregnancy weight and height) categorized as underweight (<18.5 kg/m²), overweight (25.0 to 29.9 kg/m²), or obese (≥30.0 kg/m²) compared to normal BMI (18.5 to 24.9 kg/m²).

For multiparous women, we examined the relationship between preterm birth and previous preterm birth; previous cesarean delivery; interpregnancy interval of <18 months and >59 months versus interpregnancy interval of 18–59 months. Inter-pregnancy interval was calculated from previous live birth (month and year) as reported in linked records and estimated as months to conception of the index pregnancy. Given that the day of previous live birth was not available, the middle of the month was used for calculation purposes [28].

Factors derived from hospital discharge ICD-9 diagnoses included pre-existing diabetes, pre-existing hypertension, sickle cell anemia, drug or alcohol dependence/abuse, and mental disorder (Appendix A).

Using the training dataset, a multivariable model for birth <37 weeks gestation was built using backwards-stepwise logistic regression to calculate odds ratios, where initial inclusion was determined by a threshold of $p < 0.05$ in univariable analyses. When maternal factors were protective in univariable analyses, the referent group was altered to create positive beta-coefficients. Risk scores were created for each pregnancy by adding the beta-coefficient from maternal factors in the final multivariable model. Associations with preterm birth were calculated for each risk score group (0.1 to <1.0, 1.0 to <2.0, 2.0 to <3.0, 3.0) using logistic regression with a Poisson distribution to calculate relative risks (RRs) and 95% confidence intervals (CIs) using risk score of 0.0 as the referent group. Relative risks were calculated in both the training and testing datasets. Risk scores were evaluated for the whole population and then stratified by race/ethnicity and payer (with public insurance as a proxy for low income) in the training and testing datasets.

Percent of births with other adverse maternal or infant outcomes were calculated for each risk score group. Other maternal adverse outcomes included hospital discharge diagnoses of preeclampsia, placenta previa, placental abruption, or antepartum hemorrhage (Appendix A). Adverse infant outcomes included death <28 days, small for gestational age (<10th percentile [27]), intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, or retinopathy of prematurity (Appendix A).

All analyses were performed using Statistical Analysis Software version 9.4 (Cary, NC). 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. Data used for the study were received by the University of California San Francisco by June 2016. The study was supported by the California Preterm Birth Initiative within the University of California, San Francisco.

Results

Characteristics between the women in the training ($n = 1,559,797$) and testing datasets ($n = 779,899$) did not differ significantly. Most of the women were Hispanic or White non-Hispanic, between 18 and 34 years at delivery, and had >12 years of education. For both the training and testing populations, 6.6% had a preterm birth (Table 1).

In univariable analyses of the training dataset, odds of preterm birth compared to were increased for women of color ranging from 1.2 for Hispanic and Asian women (95% CIs 1.1 to 1.2) to 1.7 for Black women (95% CI 1.7 to 1.8). Odds of preterm birth were also increased for women who were <18 or >34 years old at delivery, <12 years education, public insurance, nulliparity, BMI <18.5 or >24.9 kg/m², preexisting diabetes or hypertension, smoking or drug/alcohol use, mental illness, sickle cell anemia, previous cesarean delivery, previous preterm birth, or interpregnancy interval <18 months or >59 months. More than 12 years of education reduced the odds of a preterm birth (OR 0.9, 95% CI 0.9 to 0.9), as did birth outside of the United States (OR 0.9, 95% CI 0.9 to 0.9) (Supplemental Table S1).

For multivariable model creation, education of 12 years and mother's birth in the United States were used because both were protective in univariable calculations. In the

multivariable model, women of color had an increased odds of preterm birth, as did women who were <18 or >34 years old at delivery. Women with public insurance and women <12 years education had a slightly elevated odds of preterm birth (aOR 1.05 for both). Nulliparous, underweight, and obese women also had increased odds of preterm birth (aORs 1.06–1.29). Women with the highest odds of preterm birth included those with preexisting diabetes or hypertension, sickle cell anemia, and previous preterm birth (aOR 2.25–5.24). Mental illness, smoking, drug/alcohol use during pregnancy, a previous cesarean delivery, a short (<18 months) or long (>59 months) interpregnancy interval also increased the odds of a preterm birth (aORs 1.08–1.42) (Table 2).

Risk scores in the training sample ranged from 0.0 to 5.7 and from 0.0 to 4.8 in the training sample with the lowest scores characterized by the lack of any risk factors and the highest scores characterized by the presence of multiple risk factors. Women with a risk score of 0.1 - <1.0 were nearly two-times more likely to have a preterm birth than the women with a score of 0.0 (RR 1.9, 95% CIs 1.6–2.3, training; RR 1.8, 95% CI 1.4 to 2.3, testing). Women with a risk score of 3.0 were 12.2-times as likely to have a preterm birth in the testing dataset (95% CI 9.4 to 15.9) (Table 3). In the training dataset, 26.1% of women with a score between 2.0 - <3.0 delivered <37 weeks, and 40.6% of women with a score 3.0 had a preterm birth. This finding was replicated in the testing dataset, where 26.4% of women with a score between 2.0 - <3.0 delivered <37 weeks and 40.8% of women with a score 3.0 had a preterm birth (Fig. 1 Supplemental Table S2).

Approximately 0.2% of women with a risk score of 0.0 had a birth <32 weeks gestation in both the testing and training populations. In contrast, over 9% of the women with a risk score 3.0 had birth <32 weeks (Fig. 1, Supplemental Table S2). Although risk scores by category exhibited a pattern of increasing risk for higher versus lower risk score groupings, risk score itself was not found to be a useful classifier for preterm versus term birth with an area under the receiver operating characteristic (AUC) of 0.591 (95% CI 0.589 – 0.594) in the testing sample.

Similar to the finding for preterm birth, as risk score grouping increased, the percent of women with adverse maternal or infant outcomes other than preterm birth increased. In the testing and training datasets, 6.0 (training) to 6.8% (testing) of mothers with a risk score of 0.0 had an adverse outcome other than preterm birth. For women with a score >1.0, however, over 17% had an adverse outcome other than preterm birth. Only 41 % of women with a score 3.0 had a term delivery without preterm birth or other adverse outcome (Fig. 1, Supplemental Table S2).

When risk scores were stratified by race/ethnicity and public/ not public insurance, only White non-Hispanic women were found to have a risk scores of 0.0. Risk scores performed similarly across all race/ethnicity and income groups with women with scores 3.0 being at the highest percentage preterm birth and other adverse outcomes (Supplemental Table S3, Supplemental figure 2). Although rate of preterm birth performed similarly across race/ ethnicity and insurance groupings, there were differences in how the risk scores themselves were distributed across groupings. For example, <95.5% of Black women had risk scores less than 2.0 compared to >98% in all other racial and ethnic groups. Similarly, <0.1%

of White non-Hispanic women without public insurance had a risk score ≥ 3.0 , while 0.6% of Black women with public insurance had this score (Supplemental Table S4).

Discussion

We found that a cumulative risk score for preterm birth based on beta-coefficients for risk factors from multivariable logistic models identified women at the lowest and highest risk for preterm birth regardless of race/ethnicity or socioeconomic status. Further, we found that this cumulative risk score could also identify women at risk for other adverse outcomes who did not have a preterm birth. Most striking were our findings that women with a risk score ≥ 3.0 were more likely to have a preterm birth or other adverse outcome than they were to have a term birth without adverse outcome. Although the preterm birth risk score performed similarly across race/ethnicity and insurance groupings, there were differences in the percentages of women in each risk score group by race/ethnicity.

The present study relied on a large population-based dataset which allowed for considerable generalizability of the findings and also enabled us to examine risk scores by important subgrouping including race/ethnicity, and insurance status, and by preterm birth subtype. While the strengths of this study are notable, there were also limitations. The income of the patients, occupation, neighborhood factors, and other important markers of socioeconomic status were unavailable. As such, we used public insurance as a proxy for poverty and so it is possible that some poor women were included in the “not public insurance” stratum which would have underestimated the poverty-related burden. Additionally, we included risk factors such as smoking, drug dependence/abuse, infection, and anemia in our first-trimester models. With this administrative data, the timing of diagnosis is unknown. Therefore, we may have overestimated the contribution of these risk factors in the first-trimester. It should also be noted that information about interventions such as cerclage or progesterone therapy, which can decrease preterm birth risk [29], were not available in the dataset and thus we were unable to adjust for these factors in our models.

While other investigators have worked to create cumulative risk scores for preterm birth, ours is novel due to its size, timing, methodology and findings. For example, while Schaaf and colleagues [30] created a preterm birth prediction model using a large population that was based on maternal characteristics and obstetric factors, and developed a multivariable model for spontaneous preterm birth similar to ours. However, their investigation differed from ours in that 84.5% of their sample were White women, spontaneous preterm birth was the only outcome examined, and they did not examine the utility of the score beyond the AUC. Also of note are efforts by Goetzinger and colleagues [10] who examined whether maternal characteristics and first-trimester biomarkers could be used to predict preterm birth. Similar to our findings these investigators showed that maternal characteristics alone can be used to identify women at risk for preterm birth and importantly, showed only modest improvement with the addition of biomarkers. Also of interest, Goetzinger and colleagues [31] created risk scores for preeclampsia, where risk was weighted based on the odds ratio. Using these methods, they were able to identify women at increased risk for preeclampsia. As with previous investigations, while our methodology does not offer a population-based

preterm birth screening test, it does offer a method by which women at particularly high risk of preterm birth can be reliably identified.

It is important to note the potential clinical implications surrounding cumulative first-trimester risk scoring if validated in a clinical setting. Such scoring may identify a high risk population to consider trials with current interventions like progesterone and aspirin that have to date, mostly only been used in women with previous preterm birth, in women with shortened cervix, or in women with risk factors associated with preeclampsia [5,6,32,33]. In addition, it is possible that women at elevated cumulative risk may benefit from additional education and clinical care aimed at increasing her understanding of preterm birth and of early signs of labor. It should also be noted that a modified score based on factors such as BMI, smoking, and interpregnancy interval could be calculated before pregnancy which would allow for a focus on prevention efforts that are specific to an individual before pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Fig. 1.

Rate of preterm birth and other adverse outcome^a by risk score calculated from beta-coefficients in multivariable model for training and testing datasets: California births, 2007 to 2012.

^aOther adverse outcomes include: Preeclampsia, placenta previa, placental abruption or antepartum hemorrhage, death before discharge before 28 days, small for gestational

age(29), intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia or retinopathy of prematurity.

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Table 1

Sample characteristics.

Characteristic	Training n(%)	Testing n (%)	P- value
Sample	1,559,797	779,899	
Race or ethnicity			
White non-Hispanic	429,246 (27.5)	214,838 (27.6)	0.6565
Hispanic	738,211 (47.3)	369,232 (47.3)	0.8151
Black	77,480 (5.0)	38,747 (5.0)	0.9763
Asian	203,926 (13.1)	101,596 (13.0)	0.3138
Other ^a	110,934 (7.1)	55,486 (7.1)	0.9456
Age at delivery (years)			
Less than 18	33,996 (2.2)	17,000 (2.2)	0.9900
18 to 34	1,234,274 (79.1)	617,116 (79.1)	0.9612
More than 34	291,495 (18.7)	145,769 (18.7)	0.9595
Maternal education (years)			
Less than 12	337,107 (21.6)	168,852 (21.7)	0.5028
12	383,258 (24.6)	191,773 (24.6)	0.7573
More than 12	785,469 (50.4)	392,408 (50.3)	0.5457
Nulliparous	626,644 (40.2)	312,553 (40.1)	0.1468
Born outside of the United States	676,012 (43.3)	337,697 (43.3)	0.5640
Public insurance ^b for prenatal care	642,225 (41.2)	321,822 (41.3)	0.1827
Preterm birth	102,769 (6.6)	51,326 (6.6)	0.8273

^aIncludes: American Indian, Hawaiian or Pacific Islander, Other race, Two or more races and Unknown race or ethnicity.

^bMedi-Cal, California's Medicaid program.

^cWomen, Infants, and Children program.

Table 2

Factors in final multivariable model for births before 37 weeks^a gestation by subtype in training sample.

Maternal or obstetric factor	aOR (95%CI)	Beta-coefficient	p-value
Hispanic	1.22 (1.19, 1.24)	0.1954	< 0.0001
Black	1.52 (1.48, 1.56)	0.4182	< 0.0001
Asian	1.31 (1.28, 1.34)	0.2671	< 0.0001
Other race or ethnicity	1.32 (1.29, 1.36)	0.2774	< 0.0001
Age at delivery before 18 years	1.07 (1.03, 1.12)	0.0703	0.0015
Age at delivery more than 34 years	1.23 (1.21, 1.25)	0.2099	< 0.0001
Education less than 12 years	1.09 (1.07, 1.11)	0.0877	< 0.0001
Education equal to 12 years ^b	1.05 (1.04, 1.07)	0.0521	< 0.0001
Public insurance for prenatal care	1.05 (1.03, 1.06)	0.0464	< 0.0001
Nulliparous	1.29 (1.27, 1.31)	0.2561	< 0.0001
Mother born in United States ^b	1.12 (1.10, 1.14)	0.1138	< 0.0001
Body mass index less than 18.5 kg/m ²	1.17 (1.13, 1.20)	0.1543	< 0.0001
Body mass index 30.0 kg/m ² or more	1.06 (1.05, 1.09)	0.0656	< 0.0001
Preexisting diabetes	2.29 (2.18, 2.41)	0.8297	< 0.0001
Preexisting hypertension	3.47 (3.36, 3.58)	1.2436	< 0.0001
Smoked during pregnancy	1.25 (1.21, 1.29)	0.2194	< 0.0001
Drug or alcohol dependence or abuse	1.42 (1.36, 1.49)	0.3533	< 0.0001
Mental illness	1.41 (1.36, 1.46)	0.3403	< 0.0001
Sickle cell anemia	2.25 (1.79, 2.84)	0.8126	< 0.0001
Previous cesarean delivery	1.30 (1.28, 1.33)	0.2645	< 0.0001
Previous preterm birth	5.24 (5.01, 5.49)	1.6570	< 0.0001
Interpregnancy interval less than 18 months	1.08 (1.06, 1.11)	0.0799	< 0.0001
Interpregnancy interval 60 months	1.21 (1.18, 1.23)	0.1874	< 0.0001

aOR, adjusted odds ratio; CI, confidence interval.

^aCompared with birth between 37–42 weeks.

^bWhen maternal factors were protective in univariable models, referent was changed to make beta-coefficients positive.

Table 3

Risk of preterm birth by risk score calculated from beta-coefficients remaining in the multivariable model.

Risk score	Gestation at birth		RR (95% CI)
	Less than 37 weeks n (%)	37 weeks or more n (%)	
<u>Training</u>			
Sample			
n= 1,559,797	102,769 (6.6)	1,457,028 (93.4)	
0.0			
n = 4,153	130 (3.1)	4023 (96.9)	Reference
0.1 to less than 1.0			
n= 1,472,799	88,622 (6.0)	1,384,177 (94.0)	1.9 (1.6, 2.3)
1.0 to less than 2.0			
n = 65,536	9,333 (14.2)	56,203 (85.8)	4.5 (3.8, 5.4)
2.0 to less than 3.0			
n= 16,199	4,233 (26.1)	11,966 (73.9)	8.3 (7.0, 9.9)
3.0 or more			
n= 1,110	451 (40.6)	659 (59.4)	13.0 (10.7, 15.8)
<u>Testing</u>			
Sample			
n = 779,899	51,326 (6.6)	728,573 (93.4)	
0.0			
n = 2,093	70 (3.3)	2,023 (96.7)	Reference
0.1 to less than 1.0			
n = 736,327	44,242 (6.0)	692,085 (94.0)	1.8 (1.4, 2.3)
1.0 to less than 2.0			
n = 32,663	4,601 (14.1)	28,062 (85.9)	4.2 (3.3, 5.3)
2.0 to less than 3.0			
n = 8,191	2,158 (26.4)	6,033 (73.7)	7.9 (6.2, 10.0)
3.0 or more			
n = 625	255 (40.8)	370 (59.2)	12.2 (9.4, 15.9)

RR, Relative risk; CI, confidence interval.