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Maternal characteristics and mid-pregnancy serum biomarkers as risk factors for subtypes of preterm birth

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Abstract

Objective—To examine the relationship between maternal characteristics, serum biomarkers, and preterm birth (PTB) by spontaneous and medically-indicated subtypes.

Design—Population-based cohort.

Setting—California, United States of America.

Population—From a total population of 1,004,039 live singleton births in 2009 and 2010, 841,665 pregnancies with linked birth certificate and hospital discharge records were included.

Methods—Characteristics were compared for term and preterm deliveries by PTB subtype using logistic regression and odds ratios adjusted for maternal characteristics and obstetric factors present in final stepwise models (adjORs) and 95% confidence intervals (CIs). First and second

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Disclosure of Interests. None

Contribution to Authorship. Laura Jelliffe-Pawlowski initiated the study and provided guidance and oversight throughout all phases of the investigation including statistical analyses, manuscript writing and manuscript revision. Rebecca Baer prepared all data for analyses, conducted statistical analyses, and aided in the drafting and revision of the manuscript. Robert Currier and Gary Shaw provided guidance on study design and statistical analyses and also helped in manuscript drafting and revisions. Yair Blumenfeld, Kelli Ryckman, Hugh O’Brodivich, Jeffrey Gould, Mourice Druzin, Yasser El-Sayed, Deirdre Lyell, and David Stevenson all provided input on study design, participated in discussion about the analyses, and helped with manuscript drafting and revisions. All authors approved the final version of the submitted manuscript.

Details of ethics approval. 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 (#12-09-0702, Approval Date: 02/07/2014)

trimester serum marker levels were analyzed in a subset of 125,202 pregnancies with available first and second trimester serum biomarker results.

Main Outcome Measure—PTB by subtype.

Results—In fully adjusted models, ten characteristics and three serum biomarkers were associated with increased risk in each PTB subtype (Black race/ethnicity, preexisting hypertension with and without preeclampsia, gestational hypertension with preeclampsia, preexisting diabetes, anemia, previous PTB, one or two previous cesarean section(s), interpregnancy interval 60 months, low first trimester pregnancy-associated plasma protein A, high second trimester alpha-fetoprotein, and high second trimester dimeric inhibin A). These risks occurred in 51.6 to 86.2% of all pregnancies ending in PTB depending on subtype. The highest risk observed was for medically-indicated PTB < 32 weeks in women with preexisting hypertension and preeclampsia (adjOR 89.7, 27.3 – 111.2).

Conclusions—Our findings suggest a shared etiology across PTB subtypes. These commonalities point to targets for further study and exploration of risk reduction strategies.

Keywords

Risk factors; Spontaneous preterm birth; medically-indicated preterm birth; serum biomarkers

INTRODUCTION

Preterm birth (PTB) (< 37 weeks gestation) remains a significant individual and societal burden. While neonates with early PTB (gestational age (GA), 20 – 31 weeks) are at the highest risk for both short and long-term morbidity and mortality, neonates with late PTB (32 to 36 weeks) are also at increased risk.^{1–9} Morbidity and mortality risks have been shown to extend across PTB subtypes (spontaneous (preterm premature rupture of membranes (PPROM) or premature labor) and medically-indicated (labor induced or cesarean delivery performed because of maternal or fetal indications)).^{10–13}

Despite decades of study, few risk factors for PTB have been identified that extend across all PTB subtypes and populations. While a history of spontaneous PTB and a short cervix have been shown to be related to PTB across subtypes^{14–19} the relationship between other factors and PTB across subtypes is less well elucidated. Although a number of maternal characteristics and biomarkers (e.g. high body mass index (BMI), hypertension, diabetes, smoking, fetal fibronectin, pregnancy associated plasma protein A (PAPP-A)) have been shown to be associated with specific PTB subtypes in one or more populations,^{20–27} differences across studies in PTB definitions and consideration of subtypes has limited conclusions.^{20–27} Further elucidation of commonalities across subtypes may help us better understand the etiology of PTB and may lead to strategies aimed at reducing the cumulative burden of PTB.

Recent population-based studies in Nova Scotia and Australia, and a World Health Organization (WHO) survey of twenty-nine developed and developing countries have described patterns of risk across PTB subtypes.^{28–30} While each study approached this question somewhat differently, all three studies examined risks across subtypes and all

identified some common risk factors. For instance, all studies identified hypertension and maternal age ≥ 35 years as risk factors across subtypes. In the present study we extend this evaluation to a large population of singleton pregnancies in the United States with deliveries in California in 2009 and 2010. Like these other studies, we evaluate the relationship between a variety of maternal and obstetric factors and PTB across subtypes. We also broaden analyses to include maternal serum biomarkers that are routinely collected as part of prenatal screening for aneuploidies and neural tube defects in many developed and developing countries.^{23;31–33} Given close ties between these markers and placental function^{34–37} and the well-documented association between many of these markers and PTB,^{25;38–41} we believe these data may yield important information about risk across PTB subtypes.

METHODS

The study cohort was drawn from a population of 1,004,039 singleton pregnancies with live birth in California in 2009 and 2010. Sample selection proceeded by first identifying women with deliveries from 20 to 44 weeks based on obstetric estimate of gestation who had a linked birth certificate and hospital discharge record contained in a combined state database maintained by the California Office of Statewide Health Planning and Development ($n = 972,470$). The sample was further restricted to women with information available for race/ethnicity, age, parity, country of birth, pre-pregnancy weight, height, payer status, smoking, diabetes, hypertension, anemia, and, for multiparous women, known number of previous cesarean sections and inter-pregnancy interval available in the birth cohort file ($n = 841,665$, 83.8% of the entire population of singleton births). Coding of diabetes, hypertension, and anemia was based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)⁴² four digit codes contained in the hospital discharge database. These codes were used to classify pregnancies with preexisting diabetes (ICD-9 codes 648.0 and 250.0), gestational diabetes, 648.8, preexisting hypertension with or without preeclampsia (642.0, 642.1, 642.2, 642.7), gestational hypertension with or without preeclampsia (642.3, 642.4, 652.5, 642.6), and anemia (648.2).^{42;43}

For biomarker analyses we evaluated a subset of women in the study who had first and second trimester prenatal aneuploidy serum screening through the California Prenatal Screening Program administered by the California Genetic Disease Screening Program. By law, this screening is offered to all women seeking prenatal care between 11 and 20 weeks in California. Further details regarding the program have been described elsewhere.^{25,29}

Linkage between the combined birth certificate/hospital discharge file and prenatal screening data relied on identifiers present in both sets including mother first and last name, date of birth, address, and phone number wherein both exact and fuzzy matching of variables was allowed. Women included had expected dates of delivery in September 2009 through 2010 (final “serum marker subset” = 125,202, 14.9% of the study sample)). Restriction to only the last four months of 2009 is reflective of the start of integrated first and second trimester screening at that time.³¹ Analyte results were derived from blood samples collected between 10 weeks 0 days and 13 weeks 6 days gestation in the first trimester, and 15 weeks 0 days and 20 weeks 0 days gestation in the second trimester. First

trimester analytes measured included pregnancy-associated plasma protein A (PAPP-A) and total human chorionic gonadotropin (hCG). Second trimester analytes measured included alpha-fetoprotein (AFP), hCG, unconjugated estriol (uE3), and dimeric inhibin A (INH). Analyte levels were measured on automated equipment (Auto DELFIA, Perkin Elmer Life Sciences, Waltham, MA and Applied Biosystems, Brea, CA). All analyte results were converted to multiple of the medians (MoMs) and were adjusted for gestational age, maternal weight (as a proxy for blood volume), self-reported race/ethnicity, smoking status, and pre-existing diabetes. PTB was categorized by weeks at completed gestation (early (20 – 31 week) or late (32 – 36 weeks). Groups were further stratified by spontaneous and medically-indicated PTB. Pregnancies classified as spontaneous PTB included those where the birth certificate or hospital discharge record noted “preterm premature rupture of membranes” (PPROM) or “preterm labor”. Pregnancies with a record of receiving tocolytics with no record of PPRM were also included in the preterm labor group. Pregnancies classified as ending in medically-indicated PTB were those without PPRM or premature labor for whom there was “medical induction”, “assisted rupture of membranes”, or for whom there was a cesarean delivery < 37 weeks GA and none of the aforementioned indicators of spontaneous PTB. Pregnancies resulting in PTB without any of these specific codes were considered as having an “unknown” PTB subtype.

Logistic regression (odds ratios (ORs) and associated 95% confidence intervals (CIs)) were used to compare pregnancies resulting in early or late PPRM, preterm labor, or medically-indicated PTB to pregnancies resulting in term birth (> 37 weeks). Backward stepwise regression was used for final model building by PTB subtype, with entry into the model set at $p < 0.10$ based on crude analyses and the criteria for staying in the model set at $p < 0.05$ after adjustment for other factors. Characteristics and obstetric factors included in the analyses were race/ethnicity (Non-White race/ethnicity (by subtype)/ White race/ethnicity), maternal age (< 18-years or > 34-years/ maternal age 18–34 years), payer status (private insurance, Medi-Cal (California’s state funded medical insurance system for low-income persons), other government insurance (military or other), self-pay, no insurance, no self-pay/ private insurance), maternal education (< 12 or > 12 years/ 12 years), maternal country of birth (Mexico, Country other than Mexico/ United States), maternal body mass index (BMI) at onset of pregnancy (underweight (< 18.5), overweight (25.0 – 29.9), or obese (> 30)/ normal BMI (18.5 – 24.9)), preexisting hypertension with and without preeclampsia/ no hypertension, gestational hypertension with and without preeclampsia/ no hypertension, preexisting diabetes/ no diabetes, gestational diabetes/ no diabetes, smoking during pregnancy (yes/ no), nulliparous/ multiparous, and, among multiparous women, previous cesarean section (1, 2/ none), previous PTB (yes/ no), and inter-pregnancy interval (< 6 months, 6 – 23 months, 24 – 59 months/ 60 months/ 24 – 59 months). Inter-pregnancy interval was calculated from the report of previous live birth (reported by month and year in the birth cohort file) and estimated as months to conception of the index pregnancy. Given that the day of previous live birth was not available, the fifteenth of the month was used for IPI calculation purposes.

Chi-square was used to examine whether pregnancies in the serum marker subset differed from the in the sample cohort with respect to the occurrence of PTB (overall and by subtype), race/ethnicity, maternal age, parity, or maternal education. Logistic regression was

used to compare first trimester PAPP-A and hCG and second trimester AFP, hCG, uE3, and INH in preterm versus term pregnancies. The frequency of having a MoM the 5th or the 95th percentile versus a MoM in the 6th to 94th percentile was compared for the preterm subtype groups versus the term groups with adjustment for all characteristics found to be associated with PTB by subtype in stepwise logistic analyses for the study cohort.

All analyses were performed using Statistical Analysis Software (SAS) version 9.3 (Cary, NC) and were based on data received by the GDSP program as of June 30th, 2014. 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.

RESULTS

Most women in the sample were Hispanic or White (non-Hispanic) (52.1% Hispanic and 27.2% White) and were between 18 and 34 years of age (79.3%). The percentage of PTB based on obstetric estimate was 6.8% wherein 0.9% of births were before 32 completed weeks gestation, and 5.9% were from 32 to 36 weeks (Table 1).

Maternal risk factors present in all final subtype models included Black race/ethnicity, preexisting diabetes, preexisting hypertension with and without preeclampsia, gestational hypertension with preeclampsia, anemia, previous PTB, one or two previous cesarean section(s), and IPI $\geq$ 60 months (Tables S1 and S2, Table 2, Figure 1, Figure S1). Depending on PTB subtype, from 41.9 to 79.1% of pregnancies resulting in PTB had one or more of these risk factors present compared to 36.3% of term pregnancies (Figure S2).

Previous PTB and preexisting hypertension with preeclampsia were associated with the highest risks for PTB across groupings. Previous PTB occurred in 2.6 to 6.7% of multiparous pregnancies ending in PTB across subtypes compared to 0.7% of those ending in term birth (Table S2). After adjustment for all factors in the final stepwise models, observed risks for PTB in women with a previous PTB were at or above an adjusted OR ($_{adj}OR$) of 2.0 across groupings with the highest risks observed for premature labor 20–31 weeks ($_{adj}OR$ 8.3, 95% CI 6.5 – 10.0) and for PPROM 20–31 weeks ($_{adj}OR$ 8.0, 95% CI 6.2 – 10.3) (Table 2). Preexisting hypertension with preeclampsia occurred in 1.1 to 15.1% of pregnancies ending in PTB across subtypes versus 0.3% of term pregnancies (Table S2). Observed risk for PTB among women with preexisting hypertension with preeclampsia were also at or above an $_{adj}OR$ of 2.0 across PTB subtypes (CIs > 1.0 , $p < .05$) with the highest risks observed for medically-indicated PTB 20–31 weeks ($_{adj}OR$ 89.7 (95% CI 27.3 – 111.2) and premature labor 20–31 weeks ($_{adj}OR$ 26.7, 95% CI 23.5 – 30.2) (Table 2).

Pregnancies in the cohort with and without first and second trimester serum marker results differed by PTB rate and subtype, by race/ethnicity, by age, by parity, and by education (Table S3). For example, women with analyte results had significantly lower rates of PTB (5.4 versus 7.1%), were less likely to be Hispanic (45.3 versus 53.3%), were less likely to be Black (3.0 versus 5.8%), and were more likely to have greater than 12 years of education (62.1 versus 47.6%) (all $p < 0.05$ based on chi-square analyses). Among those with first and second trimester serum results, biomarker risks observed across PTB groupings included

first trimester PAPP-A MoM the 5th percentile, second trimester AFP MoM the 95th percentile, and second trimester INH MoM the 95th percentile. First trimester PAPP-A MoM the 5th percentile was present in 9.1 to 13.8% pregnancies ending in PTB across subtypes compared to 4.7% of pregnancies ending in term birth; second trimester AFP MoM the 95th percentile occurred in 7.5 to 18.4% of pregnancies ending in PTB across subtypes compared to 4.2% of term births; and, second trimester INH the 95th percentile was observed in 8.8 to 33.3% of pregnancies ending in PTB across subtypes compared to 4.5% of term births (Table 3, Figure S1). Risks across pregnancies with these marker abnormalities tended to be higher for early PTB across nested subtypes (e.g. PPRM, premature labor, medically-indicated) (Table 3, Figure 1). Among pregnancies with both maternal characteristic and serum biomarker data available, from 51.6 to 86.2% had one or more common characteristic or serum marker risk present, compared to 41.9% in pregnancies resulting in term births (Figure S2).

There were a number of other risks of note that were present in five of the PTB subtypes. For example, women of Hispanic race/ethnicity were at increased risk for all subtypes of PTB except late PPRM and women 35 years of age or older were at increased risk for all subtypes of PTB except early medically-indicated PTB. Also of particular note was our finding of a protective effect for IPI from 6 to 23 months across all PTB subtypes except PPRM 20 – 31 weeks (Table S4).

DISCUSSION

Main Findings

In this large population-based study of singleton pregnancies, we found that ten of the 56 maternal characteristics studied and three of the 18 serum biomarker patterns were associated with an increased risk across PTB subtypes. The highest level of risk was observed for previous PTB and for preexisting and gestational hypertension occurring with preeclampsia. Elevated risks were also consistently observed for Black race/ethnicity, preexisting hypertension occurring without preeclampsia, preexisting diabetes, anemia, previous cesarean section (one or 2), IPI 60 months, first trimester PAPP-A MoM the 5th percentile and second trimester AFP and INH MoM the 95th percentile. When evaluated in a sample of pregnancies with both characteristic and serum biomarker data, more than one in two pregnancies ending PTB, regardless of subtype or gestational timing, had one or more risk present.

While there were many commonalities in the types of risks observed across all PTB subtypes, we observed some substantial differences in the magnitude of risk associated with some specific factors. For instance, while previous PTB was associated with a five-fold or more increase in risk for PPRM and preterm labor, risks in the medically-indicated PTB groups were between two- and three-fold. Conversely, preexisting and gestational hypertension with preeclampsia were associated with risks between six- and twenty-fold for preterm labor and medically-indicated PTB whereas risks for PPRM were from 1.4 and 2.3 fold. While in most of these instances the risks observed were quite substantial, it is possible that these differences provide some subtype-specific etiologic clues..

Strengths and Limitations

While sample size and the availability of a broad range of data allowed for this first of its kind evaluation of both characteristics and serum risks across PTB subtypes and gestational ages and as such, is a potent strength, for this study we relied on data present in the birth certificate and in the hospital discharge record for categorization of PTB by subtype and for analyses related to maternal characteristics. Such reliance meant that in some instances we did not have complete data present and as such, we excluded pregnancies for which not all maternal characteristics of focus were available. Although we believe these exclusions were necessary in order to understand common risks in the context of other factors of influence, it is important to recognize this missing subset. Use of this population-based dataset also restricted our capacity for further validation of the data. While the agreement of our findings with other investigations across geographies provides some support – particularly with respect to external validity, follow-up studies that allow comparison between population-level datasets and clinic-specific comparisons are warranted. Similarly, it should be noted that the present analyses focused on association rather than prediction. Next steps would clearly benefit from an expansion of focus to prediction and possible actionable patterns using additional statistical methods. It will be important that these efforts extend beyond stepwise methods which, while useful for hypothesis generation within the groupings studied, are limited with respect to prediction and identification of causal relationships. Of high importance are follow-up studies that focus on factors that may hold the most potential for modification including, for example, anemia and IPI 60 months.

Although our examination of serum markers in a subset of pregnancies is a strength, we should note that results were present in 14.9% of the 841,665 pregnancies in the study cohort. This fraction resulted from the fact that the initiation of integrated first and second trimester prenatal screening in California began in mid-2009. While this sample is unprecedented with respect to size and the amount of data available (> 100,000), future studies that examine these patterns in a larger group of pregnancies is essential. Given that our analyte results are in strong agreement with previous published studies on PTB^{25;44–47} we expect that these results will likely persist across the overall population. Still, future studies will need to have more complete coverage of the pregnant population. Given poor coverage across all pregnancies, the present results should only be interpreted as applying to the subset of women screened.

Interpretation

Findings from this investigation both confirm and expand on those reported in other recent population-based studies.^{28–30;48} Our observation of risk across subtypes for preexisting hypertension, preexisting diabetes, and previous PTB are consistent with findings in Western Australia, Nova-Scotia, and in a recent World Health Organization (WHO) multi-country survey (Table S5).^{28–30} Our findings with respect to risk across groupings for preeclampsia and anemia are consistent with the WHO multi-country survey³² but differ somewhat from those in Australia³⁰ where investigators found that anemia was only associated with PPROM and medically-indicated PTB and found that preeclampsia was only associated with preterm labor and medically-indicated PTB.^{28–30} While it is unclear why we observed differences across all groups for anemia and preeclampsia and Australian

investigators did not, we suspect that increased power in the present study may be a contributor. It is also possible that differences are related to our being able to stratify results by early and late PTB which may have provided increased specificity of patterns and models

Of note with respect to our findings on preeclampsia is the magnitude of the association between preterm labor and preexisting hypertension with superimposed preeclampsia that we observed. The magnitude of the association observed in the present study (more than 10-fold) is much greater than has been reported in studies focused on broader PTB groupings (generally below 5-fold).^{49;50} Given that no other study that we are aware of has examined these results by PTB subtype stratified by early and later PTB, follow-up studies are warranted on this point. Further study is needed on hypertension across subtypes in general given that the magnitude of associations observed in the present study often exceeded those observed by other investigators focused on broader PTB groupings.^{28–30;51–53}

While no study that we are aware of has examined the relationship between such a broad a range of characteristics and serum factors across PTB subtypes, many of the findings presented are corroborated by other studies that have focused on specific factors and broader PTB groupings. Black race/ethnicity, IPI ≥ 60 months, low first trimester PAPP-A, high second trimester AFP, and high second trimester INH have all been found to be associated with PTB in combined PTB groupings.^{23;44–47;54–62} Our findings of higher risks in some instances by specific PTB subtypes are also well supported. For example, higher risks have been observed between obesity and early spontaneous PTB than between obesity and other subtypes and Hispanic race/ethnicity has been shown to be associated more closely with early versus later PTB.^{26;63;64} Also of particular note is our finding of an increased risk for PTB among women with a previous cesarean delivery across PTB subtypes. Given the opportunity for risk modification in some populations with unusually high cesarean rates,^{65;66} further efforts focused on this finding may be useful.

Conclusion

In this large epidemiological study we found that maternal, obstetric, and serum marker risk factors play a role in early and late PTB and in spontaneous as well as medically-indicated PTB. These findings suggest shared underlying pathways across subtypes of PTB. These commonalities point to targets for further study and exploration of risk reduction strategies that may translate across PTB subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Observed Risks: Maternal characteristics and serum marker abnormalities by preterm birth subtype.

Adj OR, adjusted odds ratio; AFP, alpha-fetoprotein; BMI, body mass index; hCG, total human chorionic gonadotropin; HTN, hypertension; INH, inhibin; IPI, interpregnancy interval; PAPP-A, pregnancy associated plasma protein A; PPRM, preterm

* Factors only presented when frequency ≥ 10 and if one or more Adj OR by subgroup

** California health program for low income persons.

*** Other government funded or military.

**** Noted as "increased" when $A_{\text{adj}}OR$ and 95% confidence interval > 1.00 and $p < .05$ or "decreased" when $A_{\text{adj}}OR < 1.00$ and $p < .05$.

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Table 1

Sample overview: Singleton pregnancies with linked birth certificate and hospital discharge records with complete data present.

	n	%
Sample	841,665	100.0
<u>Term at delivery</u>	784,064	93.2
<u>Preterm</u>		
Any	57,601	6.8
Any PPROM	12,691	1.5
Preterm Labor	30,579	3.6
Medically-Indicated	9,455	1.1
Unknown	4,876	0.6
20 – 31 weeks at delivery	7,862	0.9
Any PPROM	2,146	0.3
Preterm Labor	4,653	0.6
Medically-Indicated	850	0.1
Unknown	213	0.0
32 – 36 weeks at delivery	49,739	5.9
Any PPROM	10,545	1.3
Preterm Labor	25,926	3.1
Medically-Indicated	8,605	1.0
Unknown	4,663	0.6
<u>Race/Ethnicity</u>		
White not Hispanic	228,909	27.2
Hispanic	438,371	52.1
Black	44,993	5.4
Asian	106,047	12.6
American Indian/Alaska Native	2,836	0.3
Hawaiian/Pacific Islander	3,445	0.4
Other	527	0.1
Two or more races	16,537	2.0
<u>Maternal Age</u>		
17 years	25,660	3.1
18 – 34 years	667,160	79.3
35 years	148,845	17.7
<u>Sample Cohort</u>		
	n	%
Sample	841,665	100.0
<u>Parity after birth</u>		
1	367,828	43.7
2	473,837	56.3

<u>Maternal education</u>		
< 12 years	203,170	24.1
12 years	219,557	26.1
> 12 years	418,938	49.8

PPROM, preterm premature rupture of membranes

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Table 2

Common risk factors across all multivariate logistic models by preterm birth subtype in all California sample.

Weeks	PPROM			Preterm Labor			Medically-Indicated		
	20 – 31 Adj ^{OR*}	32 – 36 Adj ^{OR*}		20 – 31 Adj ^{OR*}	32 – 36 Adj ^{OR*}		20 – 31 Adj ^{OR*}	32 – 36 Adj ^{OR*}	
<u>Risks common across subtypes</u>									
Black race/ethnicity	2.2 (1.9 – 2.6)	1.1 (1.0 – 1.2)**		2.1 (1.9 – 2.4)	1.4 (1.3 – 1.4)		1.6 (1.3 – 2.0)	1.2 (1.1 – 1.3)	
Preexisting hypertension without preeclampsia	1.5 (1.1 – 1.9)	1.3 (1.1 – 1.5)		2.4 (2.0 – 3.0)	1.9 (1.7 – 2.1)		5.7 (3.9 – 8.3)	3.0 (2.7 – 3.5)	
Preexisting hypertension with preeclampsia	2.3 (1.5 – 3.5)	2.1 (1.6 – 2.6)		26.7 (23.5 – 30.2)	12.5 (11.5 – 13.6)		89.7 (27.3 – 111.2)	20.2 (18.1 – 22.6)	
Gestational hypertension with preeclampsia	1.4 (1.2 – 1.8)	1.5 (1.4 – 1.7)		7.2 (6.6 – 7.8)	6.9 (6.7 – 7.2)		25.5 (21.8 – 29.9)	11.7 (11.1 – 12.4)	
Preexisting diabetes	1.9 (1.5 – 2.4)	2.0 (1.8 – 2.2)		1.7 (1.3 – 2.0)	1.8 (1.7 – 2.0)		1.4 (1.1 – 1.9)	1.9 (1.7 – 2.1)	
Anemia	1.7 (1.4 – 1.9)	1.1 (1.0 – 2.0)**		1.6 (1.3 – 1.7)	1.2 (1.2 – 1.3)		1.8 (1.5 – 2.1)	1.1 (1.0 – 1.2)**	
Previous PTB	8.0 (6.2 – 10.3)	5.8 (5.1 – 6.7)		8.3 (6.5 – 10.0)	5.4 (4.9 – 5.9)		2.5 (1.3 – 4.4)	2.8 (2.3 – 3.4)	
One previous cesarean section	1.2 (1.0 – 1.4)**	1.2 (1.1 – 1.3)		1.2 (1.1 – 1.3)	1.2 (1.1 – 1.2)		1.8 (1.4 – 2.2)	2.2 (2.1 – 2.4)	
Two or more previous cesarean sections	1.6 (1.3 – 1.9)	1.3 (1.2 – 1.5)		1.6 (1.4 – 1.9)	1.5 (1.5 – 1.6)		2.4 (1.9 – 3.1)	2.9 (2.6 – 3.1)	
Interpregnancy interval 60 months	1.6 (1.4 – 1.9)	1.3 (1.2 – 1.4)		1.5 (1.3 – 1.7)	1.1 (1.0 – 1.1)**		1.2 (1.0 – 1.5)**	1.1 (1.0 – 1.1)**	

AdjOR, adjusted odds ratio; PPROM, preterm premature rupture of membranes; PTB, preterm birth.

* Each preterm subtype adjusted for all factors in final stepwise logistic models..

** p < .05

Table 3

Serum marker risks: Singleton births 2009 – 2010 with integrated screening and linked hospital discharge records (n =) by preterm subtype (n = 125,202).

Weeks	PPROM		Spontaneous, not PPROM		Medically-Indicated		Term
	20 – 31 n (%) adjOR (95% CI)*	32 – 36 n (%) adjOR (95% CI)*	20 – 31 n (%) adjOR (95% CI)*	32 – 36 n (%) adjOR (95% CI)*	20 – 31 n (%) adjOR (95% CI)*	32 – 36 n (%) adjOR (95% CI)*	37 n (%) adjOR (95% CI)*
Sample	171	1,486	412	2,973	87	1,008	118,487
First trimester							
PAPP-A**							
5 th	19 (11.1) 2.4 (1.4 – 3.8) 148 (86.6)	135 (9.1) 2.0 (1.7 – 2.5) 1,298 (87.4)	46 (11.2) 2.2 (1.6 – 3.0) 343 (83.3)	254 (8.5) 1.7 (1.5 – 1.9) 2,594 (87.3)	12 (13.8) 2.4 (1.3 – 4.5) 72 (82.8)	102 (10.1) 1.9 (1.5 – 2.4) 861 (85.4)	5,617 (4.7) 106,990 (90.3)
95 th	4 (2.3) 0.5 (0.2 – 1.3)	53 (3.6) 0.7 (0.6 – 1.0)**	23 (5.6) 1.2 (0.8 – 1.9)	125 (4.2) 0.9 (0.8 – 1.1)	3 (3.5) 0.9 (0.3 – 2.8)	45 (4.5) 1.0 (0.7 – 1.4)	Reference 5,880 (5.0)
hCG**							
5 th	14 (8.2) 1.7 (1.0 – 3.0)**	82 (5.5) 1.2 (0.9 – 1.5)	25 (6.1) 1.3 (0.9 – 2.0)	184 (6.20) 1.3 (1.1 – 1.5)	3 (3.5) 0.7 (0.2 – 2.1)	64 (6.4) 1.3 (1.0 – 1.7)**	5,645 (4.8) 106,988 (90.3)
6 th – 94 th	148 (86.6)	1,345 (90.5)	356 (86.4)	2,637 (88.7)	78 (89.7)	895 (88.8)	Reference 5,854 (4.9)
95 th	9 (5.3) 1.1 (0.5 – 2.1)	59 (4.0) 0.8 (0.6 – 1.0)**	31 (7.5) 1.4 (1.0 – 2.1)	152 (5.1) 1.0 (0.9 – 1.2)	6 (6.9) 1.2 (0.5 – 2.9)	49 (4.9) 0.9 (0.7 – 1.2)	Reference 5,022 (4.2)
Second trimester							
AFP**							
5 th	8 (4.7) 1.1 (0.5 – 2.2)	30 (2.0) 0.5 (0.3 – 0.7)	10 (2.4) 0.5 (0.3 – 1.0)	112 (3.8) 0.8 (0.6 – 0.9)	3 (3.5) 0.7 (0.2 – 2.4)	43 (4.3) 0.8 (0.6 – 1.1)	5,838 (4.9) 107,627 (90.8)
6 th – 94 th	140 (81.9)	1,276 (85.9)	335 (81.3)	2,583 (86.9)	68 (78.2)	889 (88.2)	Reference 5,022 (4.2)
95 th	23 (13.5)	180 (12.1)	67 (16.3)	278 (9.4)	16 (18.4)	76 (7.5)	Reference 5,022 (4.2)

Weeks	PPROM			Spontaneous, not PPROM			Medically-Indicated			Term
	20 – 31 n (%) adjOR (95% CI)*	32 – 36 n (%) adjOR (95% CI)*		20 – 31 n (%) adjOR (95% CI)*	32 – 36 n (%) adjOR (95% CI)*		20 – 31 n (%) adjOR (95% CI)*	32 – 36 n (%) adjOR (95% CI)*		37 n (%) adjOR (95% CI)*
Sample										
hCG**	171	1,486		412	2,973		87	1,008		118,487
5th	10 (5.9)	69 (4.6)		15 (3.6)	160 (5.4)		1 (1.2)	47 (4.7)		6,046 (5.1)
	1.2 (0.6 – 2.3)	1.0 (0.7 – 1.2)		0.8 (0.4 – 1.3)	1.1 (0.9 – 1.3)		***	0.9 (0.7 – 1.2)		
6 th – 94 th	149 (87.1)	1,338 (90.0)		349 (84.7)	2,607 (87.7)		69 (79.3)	893 (88.6)		106,927 (90.2)
95th	12 (7.0)	79 (5.3)		48 (11.7)	206 (6.9)		17 (19.5)	68 (6.8)		Reference
	1.5 (0.8 – 2.6)	1.1 (0.9 – 1.4)		2.3 (1.7 – 3.1)	1.4 (1.2 – 1.6)		3.8 (2.2 – 6.5)	1.3 (1.0 – 1.6)		5,514 (4.7)
uE3**										
5th	14 (8.2)	73 (4.9)		35 (8.5)	207 (7.0)		13 (14.9)	84 (8.3)		6,004 (5.1)
	1.7 (1.0 – 3.0)	1.0 (0.8 – 1.2)		1.8 (1.2 – 2.5)	1.4 (1.2 – 1.6)		3.3 (1.8 – 5.9)	1.7 (1.4 – 2.2)		
6 th – 94 th	144 (84.2)	1,317 (88.6)		352 (85.4)	2,583 (86.9)		71 (81.6)	866 (85.9)		106,726 (90.1)
95th	13 (7.6)	96 (6.5)		25 (6.1)	183 (6.2)		3 (3.5)	58 (5.8)		Reference
	1.6 (0.9 – 2.8)	1.4 (1.1 – 1.7)		1.2 (0.8 – 1.8)	1.3 (1.1 – 1.5)		0.7 (0.2 – 2.3)	1.2 (0.9 – 1.6)		5,757 (4.9)
INH**										
5th	8 (4.7)	59 (4.0)		13 (3.2)	146 (4.9)		0 (0.0)	40 (4.0)		6,315 (5.3)
	1.0 (0.5 – 2.1)	0.8 (0.6 – 1.0)		0.7 (0.4 – 1.3)	1.0 (0.8 – 1.2)		****	0.8 (0.6 – 1.1)		
6 th – 94 th	139 (81.3)	1,327 (89.3)		328 (79.6)	2,565 (86.3)		58 (66.7)	872 (86.5)		106,858 (90.2)
95th	24 (14.0)	100 (6.7)		71 (17.2)	262 (8.8)		29 (33.3)	96 (9.5)		Reference
	3.0 (1.9 – 4.6)	1.3 (1.1 – 1.7)		3.0 (2.3 – 3.9)	1.6 (1.4 – 1.9)		5.9 (3.7 – 9.4)	1.6 (1.3 – 2.0)		5,314 (4.5)

AdjOR, adjusted odds ratio; AFP, alpha-fetoprotein; CI, confidence interval; hCG, total human chorionic gonadotropin; INH, inhibin; PAPP-A, pregnancy-associated plasma protein A; PPROM, preterm premature rupture of membranes; PTB, preterm birth.

* Each preterm subtype adjusted for all factors in final stepwise logistic models for all California sample (Table 2).

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* Cut points for multiples of the median percentiles (all singleton pregnancies screened, 5th and 95th) were PAPP-A, 0.38 and 2.57; hCG (first-trimester), 0.50 and 1.96; AFP, 0.59 and 1.71; hCG (second-trimester), 0.41 and 2.20; unconjugated estriol, 0.63 and 1.43; inhibin, 0.54 and 2.03.

d

Not computed, n < 5.