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California Very Preterm Birth Study: design and characteristics of the population- and biospecimen bank-based nested case-control study

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Abstract

Very preterm birth (VPTB) is a leading cause of infant mortality, morbidity and racial disparity in the U.S. The underlying causes of VPTB are multiple and poorly understood. The California Very Preterm Birth Study was conducted to discover maternal and infant genetic and environmental factors associated with VPTB. This paper describes the study design, population, data and specimen collection, laboratory methods and characteristics of the study population. Using a large, population-based cohort created through record linkage of livebirths delivered from 2000 to 2007 in five counties of southern California, and existing data and banked specimens from state-wide prenatal and newborn screening, 1100 VPTB cases and 796 control mother-infant pairs were selected for study (385/200 White, 385/253 Hispanic and 330/343 Black cases/controls, respectively). Medical record abstraction of cases was conducted at over 50 hospitals to identify spontaneous VPTB, improve accuracy of gestational age, obtain relevant clinical data and exclude cases that did not meet eligibility criteria. VPTB was defined as birth at <32 weeks in Whites and Hispanics and <34 weeks in Blacks. Approximately 55% of all VPTBs were spontaneous and 45% had medical indications or other exclusions. Of the spontaneous VPTBs, approximately 41% were reported to have chorioamnionitis. While the current focus of the California Very Preterm Birth Study is to assess the role of candidate genetic markers on spontaneous VPTB, its design enables the pursuit of other research opportunities to identify social, clinical and biological determinants

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of different types of VPTB with the ultimate aim of reducing infant mortality, morbidity and racial disparities in these health outcomes in the US and elsewhere.

Keywords

Study design; California Very Preterm Birth Study

INTRODUCTION

Very preterm birth (VPTB; <32 weeks gestation) is the most frequent cause of infant mortality in the US, and is a primary contributor to long-term neurological and pulmonary disorders in children.[1–8] Infants born to Black women are disproportionately affected compared with infants born to Hispanic and non-Hispanic White women, and infants born to non-Hispanic Black women have two to three times the risk of VPTB and preterm-reltaed mortality of these other groups.[3]

Spontaneous preterm birth accounts for over two-thirds of all preterm births,[1–4] although the proportion of VPTBs that is spontaneous is not well known. The underlying causes of and racial disparities in spontaneous preterm birth are believed to be multiple and poorly understood. Social, environmental and biological factors have all been associated with spontaneous VPTB; infectious and inflammatory processes play a particularly important role among infants born very preterm.[3,9]

One of the major obstacles to preventing preterm birth and reducing racial disparities in this outcome has been our inability to identify pregnancies at greatest risk of spontaneous preterm birth and to elucidate the interactions and mechanisms of social and biological determinants. Identification of genetic factors and gene-environment interactions associated with regulation of inflammatory, immunological, endocrine and vascular processes may help improve our understanding of predisposition and pathways to preterm birth and racial disparities in this outcome.

The low prevalence of VPTB (approximately 2% of livebirths[3]) presents a challenge for aetiological and prevention research, necessitating large populations of well-characterised deliveries to obtain sufficient numbers of cases. Most genetic association studies have investigated preterm births as a homogenous group,[10–69] while few[70–76] have examined early preterm births (<34 weeks gestation) or early spontaneous preterm deliveries, which tend to have different aetiologies from late preterm or medically indicated preterm deliveries. Five out of the seven studies in the last decades had small numbers of cases (n < 60),[71–73,75,76] of which only three examined mother-infant pairs.[72,73,76] Investigations of racial and ethnic differences in genetic markers have rarely been conducted.[73,75,76]

The California Very Preterm Birth Study was initiated to evaluate maternal and infant factors associated with VPTB in three race-ethnic groups using existing large population-based prenatal and newborn specimen banks and data from screening programmes, livebirth records and hospital charts. The study is focusing on the underlying causes of spontaneous VPTB and racial disparities, including candidate maternal and infant polymorphisms, maternal-infant gene interactions, and gene-gene and gene-environment interactions. This paper describes the study design, population, data and specimen collection, laboratory methods and characteristics of the study population.

METHODS

Study design

The California Very Preterm Birth Study is comprised of three race-ethnic-specific nested case-control samples from a population-based linked cohort of women who delivered livebirths in five counties of southern California between January 2000 and April 2007. The linked cohort includes non-Hispanic White, Hispanic and Black mother-infant pairs with banked biological specimens from the California Department of Public Health's prenatal screening programme and its newborn screening programme.

The study protocol was approved by the California Health and Human Services Agency Committee for the Protection of Human Subjects (no. 05-02-01) and the Utah State University Institutional Review Board (no. 1549).

Study population

This study linked records and stored specimens collected between November 1999 and December 2006 by the California Prenatal Screening (PNS) programme to certificates of all livebirths occurring in California and to records from the California Newborn Screening (NBS) programme from January 2000 to April 2007 to generate a linked cohort for sampling of cases and controls. During the study period, the PNS programme offered voluntary triple-marker screening for chromosomal and neural tube defects to pregnant women between 15 and 20 weeks gestation.[77] Approximately 70% of women delivering livebirths in California participated in the programme. Maternal specimens leftover after screening were banked from a regional screening laboratory serving providers in San Diego, Orange and Imperial counties beginning in November 1999. In September 2003, the programme expanded to a second regional laboratory serving providers in Riverside, San Bernardino and other non-study counties. The resulting prenatal specimen bank included over 500,000 leftover specimens from all consented PNS participants in the study region. The PNS livebirth cohort was then linked to data and dried blood specimens from the NBS programme, when available. The NBS has been banking specimens leftover from testing for genetic disorders statewide since 1982.

Record linkage was conducted based on personal identifiers from birth and screening data using a probabilistic matching programme (IBM Web Sphere Quality Stage Version 7.5) and confirmed with post-match queries and clerical review. Linked records were assigned a unique study identifier and personal identifiers removed to maintain confidentiality.

Demographic and medical information available from birth and screening data were used to identify the study population (described below). Race and ethnicity were defined according to that recorded on the birth certificate; only deliveries of non-Hispanic White, Hispanic and Black women were included in the study. Mother's race-ethnicity information on California birth records has been shown to be well complete and reliable, particularly for these three groups.[78] Mother-infant pairs were classified as White if both mother and father were non-Hispanic White (hereafter referred to as White). Mother-infant pairs with a Mexican Hispanic mother and father were classified as Mexican Hispanic (hereafter referred to as Hispanic). Because paternal race-ethnicity was less complete for births to Black mothers, mother-infant pairs were classified as Black if the mother was Black, regardless of ethnicity of paternal race-ethnicity (hereafter referred to as Black). Births were initially restricted to a two-county region of California (Orange and San Diego) to minimize travel to abstract hospital records, then expanded to include three additional contiguous counties (Los Angeles, Riverside and San Bernardino) to maximize the number of births with stored specimens.

Selection of cases and controls from the linked cohort

In preparation for sampling, the linked cohort was restricted to singleton livebirths. Infants with structural malformations as identified by the California Birth Defects Monitoring Program (CBDMP) registry were excluded. Three race-ethic group-specific case-control samples were selected from the cohort, which was restricted to VPTB cases and term controls (defined below). In order to maximize statistical power with limited resources, the first eligible birth was selected for those women with more than one eligible birth, similar to a cohort design with one-time participation.

Cases of very preterm birth were identified from the linked cohort using the PNS programme gestational age estimates and the child's date of birth. VPTB was initially defined as birthweight <2500g and delivery prior to 32 weeks. PNS gestational age estimates in the linked cohort originated from early ultrasound examination (58%), self-reported last menstrual period (LMP) (36%) or physical examination ascertained prior to 20 weeks gestation (6%). Gestational age estimates were provided by clinicians to the PNS programme and routinely verified with the clinician's office for accuracy. LMP dates used by the PNS programme were collected early in pregnancy and considered more reliable than LMP dates from birth records, which were not used to assign gestational age.[79] Further abstraction of hospital charts was conducted in order to identify accurately cases of spontaneous and other types of VPTB, confirm gestational age, collect relevant clinical data and exclude cases that did not meet eligibility criteria.

Chronological case series of VPTBs were selected until the desired samples sizes were achieved to generate a representative sample for each race-ethnic group. Based on pilot abstraction of 50 VPTB cases, 385 VPTB cases were required to obtain an estimated 200 spontaneous VPTBs in each of the three race-ethnic groups. With a 1:1 case: control ratio there would be sufficient (80%) statistical power to detect associations of moderate strength (odds ratios 1.60–3.70) with spontaneous VPTB for allele frequencies ranging from 0.10 to 0.50. Because of the low proportion of Black births in the region, the case definition for Blacks was expanded to include deliveries prior to 34 weeks gestation, case and control sampling was extended to the second regional laboratory serving providers in Riverside and San Bernardino counties, and the case: control ratio was increased to 1:2 in order to obtain comparable statistical power for this group (Table 1).

Eligible controls were liveborn singleton term births (37–41 weeks gestation) with normal birthweight (≥ 2500g) and available linked prenatal and newborn screening records. Controls were excluded because of the following medical conditions reported on birth records: preeclampsia, eclampsia, placenta praevia, placental abruption, cervical cerclage and premature labour. Specified numbers of controls in each race-ethnic group were selected using simple random sampling within the same birth time period as cases. Random selection was performed using PROC SURVEYSELECT in SAS v.9.1 (SAS Inc.). Because an initial batch of Hispanic control specimens was sent for laboratory analysis prior to study expansion to additional southern California birth counties, a second sample of Hispanic controls was selected to represent the expanded geographical region.

Hospital chart review

California Birth Defects Monitoring Program conducted hospital chart reviews on behalf of the California Very Preterm Birth Study for the purpose of confirming gestational age and identifying spontaneous VPTBs. Professional medical record abstractors reviewed hospital charts of VPTBs using a structured paper abstraction form. Completed forms were reviewed and errors corrected and a subset of 60 cases was re-abstracted for validation. All data were double-key entered.

The abstraction form was developed in consultation with experienced obstetricians, gynaecologists, paediatricians and the CBDMP, and revised based on pilot testing. The form included information on medical conditions (e.g. preeclampsia, pre-pregnancy hypertension and diabetes, gestational diabetes, intrauterine growth retardation, and infectious complications such as urinary tract infections), pregnancy history, maternal height and weight, delivery details, newborn assessments, and results from any placental pathology reports.

Definition of spontaneous VPTB

For the final case definition, gestational age estimates of the VPTBs were based on PNS ultrasound-determined gestational age where available. Otherwise, gestational age was estimated from PNS LMP or, if unavailable, LMP from charts unless the LMP gestational age conflicted with the gestational age estimated from the earliest ultrasound recorded in charts, in which case the earliest chart ultrasound was used. Conflicting gestational age was defined as a difference greater than 7 days if the ultrasound was conducted in the first trimester, greater than 14 days for second trimester ultrasound and greater than 21 days for third trimester ultrasound. Gestational age for cases was reassigned if needed, based on the best available data. Cases not meeting the <32 weeks definition (or <34 weeks for Blacks) were excluded. Spontaneous VPTB cases were defined as VPTBs that had none of the following conditions reported on hospital charts: preeclampsia, ultrasound-diagnosed intrauterine growth retardation (<10^{th} percentile for given gestational age), cervical cerclage, placenta praevia at delivery, Mullerian anomaly, pregnancies achieved by assisted reproductive technologies, maternal haemoglobinopathy, placental abruption due to trauma, or other medical indications.

Biological specimens

Specimens for this study were retrieved from the California Department of Public Health, Genetic Disease Screening Program archives. As part of the PNS programme, venous blood was collected form women at 15–20 weeks gestation in programme-supplied 4-mL serum separator tubes by obstetrical care service providers and underwent expanded alpha fetoprotein testing at seven regional Newborn and Prenatal Screening (NAPS) laboratories, typically within 7 days of collection (median time = 3 days). Specimens were transported by mail under ambient conditions to regional screening laboratories. After testing, leftover specimens were refrigerated for 1–2 days and then processed using several different protocols for long-term storage. Throughout the study period, cell pellets were stored in original serum separator tubes at −20°C and serum aliquotted at time of further laboratory analysis. Between June 2000 and December 2002, serum was aliquotted at the NAPS laboratory within 1–2 days of testing into a single 40mL sterile polypropylene non-pyrogenic, cryogenic vial and stored at −20°C. Starting in January 2003, serum was aliquotted within 14 days of testing into two 1-mL sterile polypropylene non-pyrogenic, cryogenic vials and stored at −70°C. Typically, there was 1–2 mL of leftover cell pellet and 1–2mL of serum available from each woman. The PNS programme obtained written informed consistent from participants, indicating the possible research use of their specimens and data, and an option to request that their specimens not be used for research purposes.

As part of the routine NBS programme, five 14-mm diameter blood spot specimens were collected from infants on S&S filter paper by heel-stick after 12h and usually no later than 6 days of age (median age at collection for 2000–2005: 29h). Infant blood spots were dried at room temperature and transported and stored at ambient conditions for approximately 1–3 days. After routine testing, remaining specimens were placed in a −10°C to −20°C freezer at the NAPS laboratories for 2 months, then shopped in cold-packed biomailers to the central

Genetic Disease Laboratory Branch, where they were stored at 4°C before being catalogued, and repacked for long-term storage at −20°C. Typically, there are two to three 14-mm diameter blood spots leftover after testing, even for those infants requiring retesting. The NBS programme and archive covers nearly all livebirths in California. Prior to testing, all parents were provided with a privacy notification which describes the possible research use of infant specimens. Parents may make a written request to the Chief of the Genetic Disease Screening Program that their newborn's specimen not be used for such purposes.

Laboratory testing

Specimens to be tested were coded with a study identification number; laboratories were blinded to case-control status within race-ethnic group-specific batches. Samples were processed at the Center for Persons with Disabilities, Utah State University. Genomic DNA was extracted from maternal blood cell pellets and newborn dried blood spots using the GIAGEN® QIAamp® 96 Blood Kit. The DNA samples were quantified using the Invitrogen™ Quant-iT™ DNA Assay Kit. From one 3.2-mm diameter punch, we reliably extracted on average 50ng of genomic DNA. Genomic DNA from the maternal and newborn samples is currently being genotyped using the Sequenom® MassARRAY® iPLEX® platform and Applied Biosystems® Taqman® Single Nucleotide Polymorphism (SNP) assays. In addition, whole genome amplification using Phi29 polymerase[80] is used to obtain sufficient amounts of DNA for future genetic analysis from the newborn blood spots.

Selection of genes and SNPs

A literature search in PubMed database of publications before November 2009 was conducted using keywords 'maternal', 'preterm birth' and 'polymorphism' in combination with expert consultation. Over 125 key genes were identified in three overlapping pathways of interest: inflammation/immune response, coagulation/haemostasis and endocrine regulation. Approximately 1500 SNPs were selected for analysis in these genes by including tagSNPs selected to cover estimated genetic variation in both European and African popuations[81,81] as well as functional SNPs with evidence of a biological role or association with preterm birth.

RESULTS

Table 1 details the definitions used in the study for cases and controls for each race-ethnic group. The expanded case definition, sampling frame and 1:2 case: control ratio among Blacks resulted in 330 Black VPTB cases selected for chart abstraction and 343 controls [two times the 171.6 spontaneous VPTB cases anticipated based upon pilot data].

The linkage rate of prenatal screening and birth certificate data was 93%, and was slightly higher for Whites (95%) than for Blacks (92%) or Hispanic (91%). The linked file was used to generate the source population for this study. Maternal and paternal race-ethnicity information was missing for 1.5% and 6.1% of births, respectively. Missing paternal race-ethnicity was highest for births to Black mothers (13.9%, vs. 3.7% and 5.2% for births to White and Hispanic mothers, respectively).

A total of 346,456 births of all gestational ages met the race-ethnic group inclusion criteria for the study: 32.0% were White (n = 110,861), 62.7% Hispanic (n = 217,264) and 5.3% Black (n = 18,331) (Table 2). The prevalence of VPTB was higher among Blacks (2.5%) than Whites (0.8%) and Hispanics (1.1%) when gestational age was limited to <32 weeks. The prevalence for Blacks prior to 34 weeks gestation was 4.2%. After applying study exclusion criteria (Table 2, Steps 1 through 10), 1727 VPTB mother-infant pairs were identified (n = White, n = 1003 Hispanic and n = 330 Black). The chronological selection of

White and Hispanic VPTBs stopped when the target of 385 maternal-infant pairs was reached (Table 2, Step 11). A random sample of 200 White, 253 Hispanic and 343 Black controls was selected from the same race-ethnic group-specific time period as cases. Among infants of Black women, 12% of cases and 10% of controls had missing or unknown paternal race-ethnicity, and 66% had paternal race reported as Black for both cases and controls. A total of five White, two Hispanic and nine Black VPTB case mothers had subsequent eligible VPTB deliveries within their respective cohorts, and none of the selected control mothers had subsequent VPTB deliveries.

Ninety-eight percent of the linked prenatal screening livebirths were successfully linked to newborn screening records (data not shown); those that did not link included neonatal deaths that occurred prior to newborn screening. Maternal specimens of VPTB cases without newborn dried blood spots were included for maternal genotype analyses to increase statistical power and address biases that might arise from exclusion of early infant deaths (n = 142; Table 3, Step 2). In doing this, two earlier case pregnancies were identified for previously included mothers; therefore, the subsequent pregnancies were dropped (Table 3, Step 3).

Fewer than 2% (n = 19) of VPTB cases were excluded because of chart indication of multiple birth (n = 13) and/or stillbirth (n = 9) (Table 3, Step 4). An additional 3% (n = 30) were excluded because the chart-corrected gestational age was above our defined cut-offs for VPTB. The final assignment of gestational age was based on PNS ultrasound (n = 713), PNS LMP (n = 299), chart ultrasound (n = 70) or chart LMP (n = 42) (data not shown).

Table 3 summarises the final classification of cases of spontaneous VPTB based on chart review. Forty-five percent (n = 492) of VPTBs were excluded because of likely causative medical conditions leaving slightly over half (55.0%, n = 601) of VPTBs that were spontaneous (i.e. with unknown cause). All cases have maternal specimens and 87% (n = 522) also have a newborn specimen. The proportion of spontaneous VPTBs was highest in Hispanics (58.8%), 54.8% in Blacks and lowest in Whites (51.6%). The main criteria for exclusion of cases were due to pre-eclampsia (~51% of all excluded), followed by intrauterine growth retardation (~22%), cervical cerclage (~15%) and pre-labour C-section for other medical indications (~8%). The proportion of exclusions due to use of assisted reproductive technologies was higher in Whites (7.2%) than Hispanics (2.0% or Blacks (1.4%). Excluded cases among Black women had a lower percentage of Mullerian anomalies but a higher proportion of sickle cell disease compared with other racial ethnic groups.

Selected medical characteristics of cases of spontaneous VPTBs are summarized in Table 4. In each race-ethnic group, approximately half of the spontaneous VPTBs had preterm labour and approximately half had preterm premature rupture of membranes, to the extent that this can be determined through hospital records. Pre-pregnancy obesity (defined as pre-pregnancy body mass index ≥ 30kg/m^2) was the most common pre-pregnancy medical condition found among spontaneous VPTB cases; obesity was 1.5 times and three times more prevalent among Black women with spontaneous VPTB compared with Hispanic and White women, respectively. Chorioamnionitis, the most common medical complication of spontaneous VPTBs, affected approximately 40% of cases of spontaneous VPTB. Chlamydia and bacterial vaginosis were lower among White women compared with those who were Hispanic or Black.

Table 5 summarises characteristics of the final sample of spontaneous VPTB cases and controls by race-ethnic group. The proportion of White spontaneous VPTB cases occurring before 26 weeks gestation (22.2%) was lower than in Black (30.5%) and Hispanic (29.0%)

cases. The difference in proportions was larger when Blacks (similar to Hispanics and Whites) were limited to cases prior to 32 weeks gestation (42.8%, data not shown). Primiparity was more prevalent among White and Hispanic women with spontaneous VPTBs compared with Black women; the disparity in prevalence across race-ethnicity was similar among all VPTBs prior to selection of the first birth in the cohort. Male infants were somewhat more likely to be spontaneous VPTBs among White women only. The excess of White male births relative to controls was less pronounced among all White VPTBs (55.7%, data not shown) and was unaffected by the selection of the first birth in the cohort.

DISCUSSION

In this paper, the California Very Preterm Birth Study's nested case-control design, methods and study population are described. Slightly more than half of VPTBs were spontaneous (i.e. with unknown cause). Preeclampsia was the most common medical indication of VPTBs. Chorioamnionitis complicated 40% of spontaneous VPTBs. The descriptive epidemiology differed across the three race-ethnic groups studied.

The combination of prenatal and newborn screening programme data and stored specimens, linked to birth records and followed up with hospital abstraction, provides a powerful resource and method for studying VPTB. The California Very Preterm Birth Study established a large population-based, multi-year cohort of pregnancies leading to a livebirth, from which efficient, nested case-control studies can be performed. Data from charts at nearly all hospital in the region were accessed to enrich the data coming from the screening programmes and from birth records. Genetic and environmental factors can be and are currently being measured objectively in biological specimens collected from women in mid-pregnancy and from newborns soon after birth.

Important strengths of this design include minimising the selection bias that is often associated with hospital-based subject ascertainment and the time and expense of assembling a prospective cohort. The population-based sample is socio-economically diverse and consists of three different race-ethnic groups that can be analysed independently, and compared with one another, to strengthen our understanding of racial disparities and preterm birth. Biological and genomic studies of preterm birth are often hampered by lack of precision in classification of the phenotype of preterm birth and it multiple underlying social and clinical determinants. The combination of high-quality gestational age information from the prenatal screening programme, medical information from hospital charts, potential linkage to area-level social and environmental factors, and specification of spontaneous vs. indicated VPTB, enables a more precise and comprehensive assessment of VPTB. The availability of both maternal and newborn specimens broadens that analyses that can be performed to include maternal-newborn interactions as well as cross-generation gene-gene and gene-environment interactions.

Despite these strengths, there were notable challenges and limitations. Requiring a stored prenatal screening specimen limited the study to women seeking prenatal screening by 20 weeks gestation, which represents 93% of livebirths. While screening programme participants broadly represent the California birth population in terms of race-ethnicity and education, women under 20 or over 35 years of age, with late or no prenatal care, or public insurance, are less likely to participate.[79] The rate of delivery prior to 37 weeks is lower among prenatal screening participants (8.4% vs. 10% among non-participants, based on 2002 birth certificate LMP dates).[79] It is not clear how these selection factors may influence case-control comparisons.

Even though the cohort size was large, the short 3- to 7-year study time frame, lack of a closed cohort, and restriction to prenatally screened births precluded study of VPTB across a woman's entire reproductive lifespan. Selection of the first eligible birth, performed to maximize independent woman-child pairs and simulate a cohort design, resulted in a lower parity distribution within the White case-control sample: Primiparity increased from 62.3% to 66.5% among White VPTBs and from 45.5% to 53.0% among White controls. The parity distribution among Hispanics and Blacks was not affected by selection of the first eligible birth because of the low rate of repeat eligible births in their respective cohorts (3% and 7% respectively, vs. 16% among Whites). The impact of this bias on genetic findings within the White case-controls ample will be evaluated by limiting the analyses to the first 2 years of data or to primiparous women[83] and comparing the results with those obtained with the full White case group.

The definition of VPTB was inconsistent for infants of Black women because of relatively small numbers in the study population. That definition was expanded from births <32 to <34 weeks gestation, creating potential problems in cross-race-ethnic group comparisons. While data abstraction all over 50 hospital facilities was a strength of our study, clinical data were not collected prospectively in a standardized fashion. Chart review was done primarily to determine whether a VPTB identified through initial screening was a spontaneous as opposed to a non-spontaneous preterm birth. Because chart review was not done for controls, adjustment variables were limited and exclusion of controls was based on birth certificate data, which has low sensitivity for medical complications.[84–86] Behavioural factors, such as exercise, sleep and diet, are not available for existing data sources; however, others such as smoking and caffeine consumption, can be measured using biomarkers. The types of laboratory methods used and the choice of biomarkers studied must be evaluated and tailored to the limited quantity and quality of specimens processed for routine clinical purposes.

While the current focus of the California Very Preterm Birth Study is to assess the role of candidate genetic markers on spontaneous VPTB, its design enables the pursuit of many other research opportunities to identify the determinants of other types of VPTB. Addresses from the prenatal and delivery period, obtained from prenatal and newborn screening, hospital charts, and birth records, are currently being geocoded and linked to US Census and other data to characterise social and environmental area-level factors. Of particular promise is the availability of maternal serum specimens in both cases and controls to investigate serological markers such as antibodies, environmental exposures and angiogenesis related factors, and their association with different types of VPTBs. Banked biological material from the California Very Preterm Birth Study can be used to replicate future findings from other research groups and to support collaborative genome-wide association and other studies demanding large numbers of VPTB cases. In these ways, the California Very Preterm Birth Study provides a strong platform to investigate racial and ethnic disparities and the leading causes of infant mortality in the US today.

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and Marissa Root assisted with project coordination. Dr. Michael S. Kramer gave valuable input on the early development of the abstraction form and F. Carol Bruce gave feedback on the conduct of the study.

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References

1. Anum EA, Springel EH, Shriver MD, Strauss JF. Genetic contributions to disparities in preterm birth. Pediatric Research. 2009; 65:1–9. [PubMed: 18787421]
2. Whitehead NS, Callaghan W, Johnson C, Williams L. Racial, ethnic, and economic disparities in the prevalence of pregnancy complications. Maternal and Child Health Journal. 2009; 13:198–205. [PubMed: 18484175]
3. Kramer MR, Hogue CR. What causes racial disparities in very preterm birth? A biosocial perspective. Epidemiologic Reviews. 2009; 31:84–98. [PubMed: 19477907]
4. Williamson DM, Abe K, Bean C, Ferre C, Henderson Z, Lackritz E. Current research in preterm birth. Journal of Women's Health. 2008; 17:1545–1549.
5. Cockle JV, Gopichandran N, Walker J, Levene MI, Orsi NM. Matrix metalloproteinases and their tissue inhibitors in preterm perinatal complications. Reproductive Sciences. 2007; 14:629–645. [PubMed: 18000225]
6. Buhimschi CS, Weiner CP, Buhimschi IA. Clinical proteomics: a novel diagnostic tool for the new biology of preterm labor, part I: proteomic tools. Obstetrical & Gynecological Survey. 2006; 61:481–486. [PubMed: 16787551]
7. Giarratano G. Genetic influences on preterm birth. MCN The American Journal of Maternal/Child Nursing. 2006; 31:169–175.
8. Dizon-Townson DS, Major H, Varner M, Ward K. A promoter mutation that increases transcription of the tumor necrosis factor-a gene is not associated with preterm delivery. American Journal of Obstetrics and Gynecology. 1997; 177:810–813. [PubMed: 9369824]
9. Behrman, RE.; Butler, AS., editors. Preterm Birth Causes, Consequences, and Prevention. Vol. Chapter 6. Washington, D.C: The National Academies Press; 2007. Biological pathways leading to preterm birth; p. 169-206.
10. Romero R, Friel LA, Velez Edwards DR, Kusanovic JP, Hassan SS, Mazaki-Tovi S, et al. A genetic association study of maternal and fetal candidate genes that predispose to preterm prelabor rupture of membranes (PROM). American Journal of Obstetrics and Gynecology. 2010; 203:361.e1–e30. [PubMed: 20673868]
11. Romero R, Velez Edwards DR, Kusanovic JP, Hassan SS, Mazaki-Tovi S, Vaisbuch E, et al. Identification of fetal and maternal single nucleotide polymorphisms in candidate genes that predispose to spontaneous preterm labor with intact membranes. American Journal of Obstetrics and Gynecology. 2010; 202:431.e1–e34. [PubMed: 20452482]
12. Gargano JW, Holzman CB, Senagore PK, Reuss L, Pathak DR, Friderici KH, et al. Polymorphisms in thrombophilia and rennin-angiotensin system pathways, preterm delivery, and evidence of placental hemorrhage. American Journal of Obstetrics and Gynecology. 2009; 201:317.e1–e9. [PubMed: 19733287]
13. Kramer MS, Kahn SR, Rozen R, Evans R, Platt RW, Chen MF, et al. Vasculopathic and thrombophilic risk factors for spontaneous preterm birth. International Journal of Epidemiology. 2009; 38:715–723. [PubMed: 19336437]
14. Tsai HJ, Yu Y, Zhang S, Pearson C, Ortiz K, Xu X, et al. Association of genetic ancestry with preterm delivery and related traits among African American mothers. American Journal of Obstetrics and Gynecology. 2009; 201:94.e1–e10. [PubMed: 19446788]
15. Velez DR, Fortunato S, Thorsen P, Lombardi SJ, Williams SM, Menon R. Spontaneous preterm birth in African Americans is associated with infection and inflammatory response gene variants. American Journal of Obstetrics and Gynecology. 2009; 200:209.e1–e27. [PubMed: 19019335]
16. Yu Y, Tsai HJ, Liu X, Mestan K, Zhang S, Pearson C, et al. The joint association between F5 gene polymorphisms and maternal smoking during pregnancy on preterm delivery. Human Genetics. 2009; 124:659–668. [PubMed: 19020903]

17. Chaves JHB, Babayan A, Bezerra CdM, Linhares IM, Witkin SS. Maternal and neonatal interleukin-1 receptor antagonist genotype and pregnancy outcomes in a population with a high rate of pre-term birth. American Journal of Reproductive Immunology. 2008; 60:312–317. [PubMed: 18754838]

18. Diaz-Cueto L, Dominguez-Lopez P, Cantillo-Cabarcas J, Perez-Figueroa G, Arechavaleta-Velasco M, Arechavaleta-Velasco F. Progesterone receptor gene polymorphisms are not associated with preterm births in a Hispanic population. International Journal of Gynaecology and Obstetrics. 2008; 103:153–157. [PubMed: 18722616]

19. Fortunato SJ, Menon R, Velez DR, Thorsen P, Williams SM. Racial disparity in maternal-fetal genetic epistasis in spontaneous preterm birth. American Journal of Obstetrics and Gynecology. 2008; 198:666.e1–e10. [PubMed: 18538149]

20. Hollegaard MV, Grove J, Thorsen P, Wang X, Mandrup S, Christiansen M, et al. Polymorphisms in the tumor necrosis factor alpha and interleukin 1-beta promoters with possible gene regulatory functions increase the risk of preterm birth. Acta Obstetricia et Gynecologica Scandinavica. 2008; 87:1285–1290. [PubMed: 18951205]

21. Luo G, Morgan T, Bahtiyar MO, Snegovskikh VV, Schatz F, Kuczynski E, et al. Single nucleotide polymorphisms in the human progesterone receptor gene and spontaneous preterm birth. Reproductive Sciences. 2008; 15:147–155. [PubMed: 18276950]

22. Uma R, Forsyth JS, Struthers AD, Frase CG, Godfrey V, Murphy DJ. Correlation of angiotensin converting enzyme activity and the genotypes of the I/D polymorphism in the ACE gene with preterm birth and birth weight. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2008; 141:27–30.

23. Velez DR, Fortunato SJ, Thorsen P, Lombardi SJ, Williams SM, Menon R. Preterm birth in Caucasians is associated with coagulation and inflammation pathway gene variants. PLoS ONE. 2008; 3:e3283. [PubMed: 18818748]

24. Velez DR, Fortunato SJ, Williams SM, Menon R. Interleukin-6 (IL-6) and receptor (IL6-R) gene haplotypes associate with amniotic fluid protein concentrations in preterm birth. Human Molecular Genetics. 2008; 17:1619–1630. [PubMed: 18276608]

25. Velez DR, Menon R, Thorsen P, Jiang L, Simhan H, Morgan N, et al. Ethnic differences in interleukin 6 (IL-6) and IL6 receptor genes in spontaneous preterm birth and effects on amniotic fluid protein levels. Annals of Human Genetics. 2007; 71:586–600. [PubMed: 17346257]

26. Chen BH, Carmichael SL, Shaw GM, Iovannisci DM, Lammer EJ. Association between 49 infant gene polymorphisms and preterm delivery. American Journal of Medical Genetics Part A. 2007; 143A:1990–1996. [PubMed: 17676631]

27. Gibson CA, MacLennan AH, Dekker GA, Goldwater PN, Dambrosia JM, Munroe DJ, et al. Genetic polymorphisms and spontaneous preterm birth. Obstetrics and Gynecology. 2007; 109:384–391. [PubMed: 17267840]

28. Gibson CS, MacLennan AH, Janssen NG, Kist WJ, Hague WM, Haan EA, et al. Associations between fetal inherited thrombophilia and adverse pregnancy outcomes. American Journal of Obstetrics and Gynecology. 2006; 194:947.e1–947.e10. [PubMed: 16580281]

29. Grisaru-Granovsky S, Tevet A, Bar-Shavit R, Salah Z, Elstein D, Samueloff A, et al. Association study of protease activated receptor 1 gene polymorphisms and adverse pregnancy outcomes: results of a pilot study in Israel. American Journal of Medical Genetics Part A. 2007; 143A:2557–2563. [PubMed: 17935246]

30. Meirhaeghe A, Boreham CAG, Murray LJ, Richard F, Smith GD, Young IS, et al. A possible role for the PPARG Pro12Ala polymorphism in preterm birth. Diabetes. 2007; 56:494–498. [PubMed: 17259396]

31. Stonek F, Hafner E, Philpp K, Hefler LA, Bentz EK, Tempfer CB. Methylenetetrahydrofolatereductase C677T polymorphism and pregnancy complications. Obstetrics and Gynecology. 2007; 110:363–368. [PubMed: 17666612]

32. Valdez-Velazquez L, Quintero-Ramos A, Perez SA, Mendoza-Carrera F, Montoya-Fuentes H, Rivas F Jr, et al. Genetic polymorphisms of the rennin-angiotensin system in preterm delivery and premature rupture of membranes. Journal of the Renin-Angiotensin-Aldosterone System. 2007; 8:160–168. [PubMed: 18205094]

33. Bodamer OA, Mitterer G, Maurer W, Pollak A, Mueller MW, Schmidt WM. Evidence for an association between mannose-binding lectin 2 (MBL2) gene polymorphisms and pre-term birth. Genetics in Medicine. 2006; 8:518–524. [PubMed: 16912583]
34. Engel SM, Olshan AF, Siega-Riz AM, Savitz DA, Chanock SJ. Polymorphisms in folate metabolizing genes and risk for spontaneous preterm and small-for-gestational age birth. American Journal of Obstetrics and Gynecology. 2006; 195:1231, e1–e11. [PubMed: 17074544]
35. Erichsen HC, Mulherin Engel SA, Eck PK, Welch R, Yeager M, Levine M, et al. Genetic variation in the sodium-dependent vitamin C transporters, SLC23A1, and SLC23A2 and risk for preterm delivery. American Journal of Epidemiology. 2006; 163:245–254. [PubMed: 16357110]
36. Kalish RB, Vardhana S, Normand NJ, Gupta M, Witkin SS. Association of a maternal CD14 -159 gene polymorphism with preterm premature rupture of membranes and spontaneous preterm birth in multi-fetal pregnancies. Journal of Reproductive Immunology. 2006; 70:109–117. [PubMed: 16427140]
37. Kalish RB, Nguyen DP, Vardhana S, Gupta M, Perni SC, Witkin SS. A single nucleotide A>G polymorphism at position −670 in the Fas gene promoter: relationship to preterm premature rupture of fetal membranes in multifetal pregnancies. American Journal of Obstetrics and Gynecology. 2005; 192:208–212. [PubMed: 15672026]
38. Kalish RB, Vardhana S, Gupta M, Perni SC, Witkin SS. Interleukin-4 and -10 gene polymorphisms and spontaneous preterm birth in multifetal gestations. American Journal of Obstetrics and Gynecology. 2004; 190:702–706. [PubMed: 15042002]
39. Kalish RB, Vardhana S, Gupta M, Perni SC, Chasen ST, Witkin SS. Polymorphisms in the tumore necrosis factor-a gene at position −308 and the inducible 70 kd heat shock protein gene at position +1267 in multifetal pregnancies and preterm premature rupture of fetal membranes. American Journal of Obstetrics and Gynecology. 2004; 191:1368–1374. [PubMed: 15507967]
40. Kalish RB, Vardhana S, Gupta M, Chasen ST, Perni SC, Witkin SS. Interleukin-1 receptor antagonist gene polymorphism and multifetal pregnancy outcome. American Journal of Obstetrics and Gynecology. 2003; 189:911–914. [PubMed: 14586324]
41. Mattar R, de Souza E, Daher S. Preterm delivery and cytokine gene polymorphisms. The Journal of Reproductive Medicine. 2006; 51:317–320. [PubMed: 16737028]
42. Menon R, Velez DR, Simhan H, Ryckman K, Jiang L, Thorsen P, et al. Multilocus interactions at maternal tumor necrosis factor-a, tumor necrosis factor receptors, interleukin-6 and interleukin-6 receptor genes predict spontaneous preterm labor in European-American women. American Journal of Obstetrics and Gynecology. 2006; 194:1616–1624. [PubMed: 16731080]
43. Menon R, Velez DR, Thorsen P, Vogel I, Jacobsson B, Williams SM, et al. Ethnic differences in key candidate genes for spontaneous preterm birth: TNF-a and its receptors. Human Heredity. 2006; 62:107–118. [PubMed: 17047334]
44. Murtha AP, Nieves A, Hauser ER, Swamy GK, Yonish BA, Sinclair TR, et al. Association of maternal IL-1 receptor antagonist intron 2 gene polymorphism and preterm birth. American Journal of Obstetrics and Gynecology. 2006; 195:1249–1253. [PubMed: 17074546]
45. Speer EM, Gentile DA, Zeevi A, Pillage G, Huo D, Skoner DP. Role of single nucleotide polymorphisms of cytokine genes in spontaneous preterm delivery. Human Immunology. 2006; 67:915–923. [PubMed: 17145371]
46. Wang H, Parry S, Macones G, Sammel M, Kuivaniemi H, Tromp G, et al. A functional SNP in the promoter of the SERPINH1 gene increases risk of preterm premature rupture of membranes in African Americans. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103:13463–13467. [PubMed: 16938879]
47. Fuks A, Parton LA, Polavarapu S, Netta D, Strassberg S, Godi I, et al. Polymorphism of Fas and Fas ligand in preterm premature rupture of membranes in singleton pregnancies. American Journal of Obstetrics and Gynecology. 2005; 193:1132–1136. [PubMed: 16157125]
48. Hartel C, von Otte S, Koch J, Ahrens P, Kattner E, Segerer H, et al. Polymorphisms of haemostasisgenees as risk factor for preterm delivery. Journal of Thrombosis and Haemostasis. 2005; 94:88–92.

49. Hartel C, Finas D, Ahrens P, Kattner E, Schaible TH, Muller D, et al. Polymorphisms of genes involved in innate immunity: association with preterm delivery. Molecular Human Reproduction. 2004; 10:911–915. [PubMed: 15516360]
50. Johnson WG, Scholl TO, Spychala JR, Buyske S, Stenroos E, Chen X. Common dihydrofolatereductase 19-base pair deletion allele: a novel risk factor for preterm delivery. American Journal of Clinical Nutrition. 2005; 81:664–668. [PubMed: 15755837]
51. Bessler H, Osovsky M, Sirota L. Association between IL-1ra gene polymorphism and premature delivery. Biology of the Neonate. 2004; 85:179–183. [PubMed: 14673228]
52. Doh K, Sziller I, Vardhana S, Kovacs E, Papp Z, Witkin SS. 2-adrenergic receptor gene polymorphisms and pregnancy outcome. Journal of Perinatal Medicine. 2004; 32:413–417. [PubMed: 15493717]
53. Genc MR, Onderdonk AB, Vardhana S, Delaney ML, Norwitz ER, Tuomala RE, et al. Polymorphism in intron 2 of the interleukin-1 receptor antagonist gene, local midtrimester cytokine response to vaginal flora, and subsequent preterm birth. American Journal of Obstetrics and Gynecology. 2004; 191:1324–1330. [PubMed: 15507961]
54. Hao K, Wang X, Niu T, Xu X, Li A, Chang W, et al. A candidate gene association study on preterm delivery: application of high-throughput genotyping technology and advanced statistical methods. Human Molecular Genetics. 2004; 13:683–691. [PubMed: 14976157]
55. Macones GA, Parry S, Elkousy M, Clothier B, Ural SH, Strauss JF. A polymorphism in the promoter region of TNF and bacterial vaginosis: preliminary evidence of gene-environment interaction in the etiology of spontaneous preterm birth. American Journal of Obstetrics and Gynecology. 2004; 190:1504–1508. [PubMed: 15284722]
56. Moore S, Ide M, Randhawa M, Walker JJ, Reid JG, Simpson NAB. An investigation into the association among preterm birth cytokine gene polymorphisms and periodontal disease. BJOG. 2004; 111:125–132. [PubMed: 14723749]
57. Nukui T, Day RD, Sims CS, Ness RB, Romkes M. Maternal/newborn GSTT1 null genotype contributes to risk of preterm, low birthweight infants. Pharmacogenetics. 2004; 14:569–576. [PubMed: 15475730]
58. Papazoglou D, Galazios G, Koukourakis MI, Kontomanolis EN, Maltezos E. Association of -634G/C and 936C/T polymorphism of the vascular endothelial growth factor with spontaneous preterm delivery. Acta Obstetricia et Gynecologica Scandinavica. 2004; 83:461–465. [PubMed: 15059159]
59. Resch B, Gallistl S, Kutschera J, Mannhalter C, Muntean W, Mueller WD. Thrombophilic polymorphisms – factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolatereductase C677T mutations – and preterm birth. Wiener Klinische Wochenschrift. 2004; 116:622–626. [PubMed: 15515881]
60. Valdez LL, Quintero A, Garcia E, Olivares N, Celis A, Rivas F, et al. Thrombophilic polymorphisms in preterm delivery. Blood Cells, Molecules & Diseases. 2004; 33:51–56.
61. Wang H, Parry S, Macones G, Sammel MD, Ferrand PE, Kuivaniemi H, et al. Functionally significant SNP MMP3 promoter haplotypes and preterm premature rupture of membranes (PPROM). Human Molecular Genetics. 2004; 13:2659–2669. [PubMed: 15367487]
62. Ferrand PE, Parry S, Sammel M, Macones GA, Kuivaniemi H, Romero R, et al. A polymorphism in the matrix metalloproteinase-9 promoter is associated with increased risk of preterm premature rupture of membranes in African Americans. Molecular Human Reproduction. 2002; 8:494–501. [PubMed: 11994547]
63. Ferrand PE, Fujimoto T, Chennathukuzhi V, Parry S, Macones GA, Sammel M, et al. The CARD15 293insC mutation and TLR4 896 A>G polymorphism in African Americans and risk of preterm premature rupture of membranes (PPROM). Molecular Human Reproduction. 2002; 8:1031–1034. [PubMed: 12397216]
64. Fujimoto T, Parry S, Urbanek M, Sammel M, Macones G, Kuivaniemi H, et al. A single nucleotide polymorphism in the matrix metalloproteinase-1 (MMP-1) promoter influences amnion cell MMP-1 expression and risk for preterm premature rupture of the fetal membranes. The Journal of Biological Chemistry. 2002; 277:6296–6302. [PubMed: 11741975]

65. Landau R, Xie HG, Dishy V, Stein M, Wood AJJ, Moore JH, et al. b2-adremergic receptor genotype and preterm delivery. American Journal of Obstetrics and Gynecology. 2002; 187:1294–1298. [PubMed: 12439523]
66. Lorenz E, Hallman M, Marttila R, Haataja R, Schwartz DA. Association between the Asp299Gly polymorphisms in the toll-like receptor 4 and premature births in the Finnish population. Pediatric Research. 2002; 52:373–376. [PubMed: 12193670]
67. Ozkur M, Dogulu F, Ozkur A, Gokmen B, Inaloz SS, Aynacioglu AS. Association of the Gln27Glu polymorphism of the beta-2-adrenergic receptor with preterm labor. International Journal of Gynaecology and Obstetrics. 2002; 77:209–215. [PubMed: 12065131]
68. Wang X, Zuckerman B, Pearson C, Kaufman G, Chen C, Wang G, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. JAMA. 2002; 287:195–202. [PubMed: 11779261]
69. Aidoo M, McElroy PD, Kolczk MS, Terlouw DJ, Kuile FO, Nahlen B, et al. Tumor necrosis factor-a promoter variant 2 (TNF2) is associated with preterm delivery, infant mortality, and malaria morbidity in western Kenya: Asembo Bay Cohort Project IX. Genetic Epidemiology. 2001; 21:201–211. [PubMed: 11668577]
70. Rey G, Skowronek F, Alciaturi J, Alonso J, Bertoni B, Sapiro R. Tool receptor 4 Asp299Gly polymorphism and its association with preterm birth and premature rupture of membranes in a South American population. Molecular Human Reproduction. 2008; 14:555–559. [PubMed: 18723631]
71. Ameglio F, Vento G, Romagnoli C, Giardina B, Capoluongo E. Association of MBL2 variants with early preterm delivery. Genetics in Medicine. 2007; 9:136–137. [PubMed: 17304056]
72. Kerk J, Dordelmann M, Bartels DB, Brinkhaus MJ, Dammann CEL, Dork T, et al. Mulitplex measurement of cytokine/receptor gene polymorphisms and interaction between interleukin-10 (−1082) genotype and chorioamnionitis in extreme preterm delivery. Journal of the Society for Gynecologic Investigation. 2006; 13:350–356. [PubMed: 16814164]
73. Amory JH, Adams KM, Lin MT, Hansen JA, Eschenbach DA, Hitti J. Adverse outcomes after preterm labor are associated with tumor necrosis factor-a polymorphism -863, but not -308, in mother-infant pairs. American Journal of Obstetrics and Gynecology. 2004; 191:1362–1367. [PubMed: 15507966]
74. Annells MF, Hart PH, Mullighan CG, Heatley SL, Robinson JS, Bardy P, et al. Interleukins-1, -4, -6, -10, tumor necrosis factor transforming growth factor-b, FAS, and mannose-binding protein C gene polymorphisms in Australian women: risk for preterm birth. American Journal of Obstetrics and Gynecology. 2004; 191:2056–2067. [PubMed: 15592292]
75. Simhan HN, Krohn MA, Roberts JM, Zeevi A, Cartitis SN. Interleukin-6 promoter – 174 polymorphism and spontaneous preterm birth. American Journal of Obstetrics and Gynecology. 2003; 189:915–918. [PubMed: 14586325]
76. Genc MR, Gerber S, Nesin M, Witkin SS. Polymorphism in the interleukin-1 gene complex and spontaneous preterm delivery. American Journal of Obstetrics and Gynecology. 2002; 187:157–163. [PubMed: 12114904]
77. Cunningham GC. Cost and effectiveness of the California triple marker prenatal screening program. Genetics in Medicine. 1999; 1:200–207.
78. Baumeister L, Marchi K, Pearl M, Williams R, Braveman P. Validation of racial/ethnic information in California birth certificates. Health Services Research. 2000; 35:869–883. [PubMed: 11055453]
79. Pearl M, Wier M, Kharrazi M. Assessing the quality of last menstrual period date on California birth records. Paediatric and Perinatal Epidemiology. 2007; 21:50–61. [PubMed: 17803618]
80. Dean FB, Hosono S, Fang L, Wu X, Faruqi AF, Bray-Ward P, et al. Comprehensive human genome amplification using multiple displacement amplification. Proceedings of the National Academy of Sciences of the United States of America. 2002; 99:5261–5266. [PubMed: 11959976]
81. Carlson CS, Eberle MA, Rieder MJ, Yi Q, Kruglyak L, Nickerson DA. Selecting a maximally informative set of single-nucleotide polymorphisms for association analyses using linkage disequilibrium. American Journal of Human Genetics. 2004; 74:106–120. [PubMed: 14681826]

82. Howie BN, Carlson CS, Rieder MJ, Nickerson DA. Efficient selection of tagging single-nucleotide polymorphisms in multiple populations. Human Genetics. 2006; 120:58–68. [PubMed: 16680432]

83. Olsen J. Options in making use of pregnancy history in planning and analysing studies of reproductive failure. Journal of Epidemiology and Community Health. 1994; 48:171–174. [PubMed: 8189173]

84. Montgomery T, Lewis A, Hammes L. Live birth certificates; evaluation of medical and health data in California. California Medicine. 1962; 96:190–195. [PubMed: 14475552]

85. Roohan PJ, Josberger RE, Acar J, Dabir P, Feder HM, Gagliano PJ. Validation of birth certificate data in New York State. Journal of Community Health. 2003; 28:335–346. [PubMed: 14535599]

86. Lydon-Rochelle MT, Holt VL, Cárdenas V, Nelson JC, Easterling TR, Gardella C, et al. The reporting of pre-existing maternal medical conditions and complications of pregnancy on birth certificates and in hospital discharge data. American Journal of Obstetrics and Gynecology. 2005; 193:125–134. [PubMed: 16021070]

Table 1

Summary of study design, with definitions of very preterm birth (VPTB) cases and controls for three race-ethnic groups: singleton livebirths delivered in five south California counties[a], California Very Preterm Birth Study

	White	Hispanic	Black
Maternal race-ethnicity	Non-Hispanic White	Mexican Hispanic White	Black of any ethnicity
Paternal race-ethnicity	Non-Hispanic White	Mexican Hispanic White	Any race-ethnicity
Maternal specimen testing laboratories[b]	Regional laboratory 1	Regional laboratory 1	Regional laboratories 1 & 2
Maternal specimen collection period	Nov. 1999–Oct. 2006	Nov. 1999–Sept. 2002	Nov. 1999–Dec. 2006
Gestational age (completed weeks)	Cases: 20–31	Cases: 20–31	Cases: 20–33
	Controls: 37–41	Controls: 37–41	Controls: 37–41
Birthweight (g)	Cases: <2500	Cases: <2500	Cases: <2500
	Controls:≥ 2500	Controls:≥ 2500	Controls:≥ 2500
Total number of VPTBs, all cases and types, with newborn specimens	385	385	330
Expected number of spontaneous VPTB cases[c]	200	200	172
Case: control ratio	1:1	1:1	1:2
Number of controls	200	200	343

[a] Los Angeles, Orange, Riverside, San Bernardino and San Diego.

[b] Regional laboratory 1 was located in Long Beach and served providers in San Diego, Orange and Imperial Counties. Regional laboratory 2 was located in Fresno and served providers in San Bernardino and Riverside counties, as well as counties outside southern California.

[c] Based on pilot data, 52% of VPTBs were expected to be spontaneous VPTBs.

Table 2

Derivation of study population: very preterm births (VPTBs) selected for chart abstraction and controls from the linked prenatal screening livebirth cohort of 346 456 by race-ethnic group, California Very Preterm Birth Study

	White (*n* = 110,861)		Hispanic (*n* = 217,264)		Black (*n* = 18,331)	
	VPTBs	Controls	VPTBs	Controls	VPTBs	Controls
Inclusion steps	*n* (%)[a]	*n* (%)[a]	*n* (%)[a]	*n* (%)[a]	*n* (%)[a]	*n* (%)[a]
1. Gestational age <32 weeks (<34 weeks for Blacks) for VPTBs; controls ≥ 37 weeks	929 (NA)	99 981 (NA)	2439 (NA)	194 676 (NA)	774 (NA)	15 582 (NA)
2. Singletons (based on birth certificate)	691 (74.4)	98 778 (98.8)	2085 (85.5)	193 266 (99.3)	643 (83.1)	15 421 (99.0)
3. Birthweight <2500 g for VPTBs and ≥ 2500 g for controls	674 (97.5)	97 672 (98.9)	1942 (93.1)	190 462 (98.5)	590 (91.8)	14 908 (96.7)
4. Link to Newborn Screening Specimen	597 (88.6)	96 783 (99.1)	1733 (89.2)	188 973 (99.2)	517 (87.6)	14 624 (98.1)
5. Maternal specimens collected by regional laboratory #1 (Blacks also include regional laboratory #2)	458 (76.7)	78 893 (81.5)	1123 (64.8)	124 885 (66.1)	517 (100)	14 624 (100)
6. Born in Los Angeles, Orange, Riverside, San Bernardino or San Diego counties	445 (97.2)	77 579 (98.3)	1086 (96.7)	118 829 (95.2)	407 (78.7)	11 643 (79.6)
7. No. of eligible controls not excluded for complications of pregnancy or delivery	NA (NA)	74 632 (96.2)	NA (NA)	116 008 (97.6)	NA (NA)	11 237 (96.5)
8. First pregnancy during study period	421 (94.6)	63 879 (85.6)	1035 (95.3)	104 845 (90.4)	384 (94.3)	10 433 (92.8)
9. No birth defects identified by CBDMP registry	405 (96.2)	63 874 (100)	1026 (99.1)	104 839 (100)	380 (99.0)	10 427 (99.9)
10. Stored maternal specimens available	394 (97.3)	63 265 (99.0)	1003 (97.8)	104 061 (99.3)	330 (86.8)	9116 (87.4)
11. First 385 VPTBs of Whites and Hispanics, all available Black VPTBs, and random samples of controls	385 (NA)	200 (NA)	385 (NA)	253[b] (NA)	330 (NA)	343 (NA)

[a] % of remaining.

[b] Because of expansion of the study region after the shipping and DNA extraction of Hispanic specimens, 53 extra Hispanic controls were sampled to represent the expanded geographical region.

NA, not applicable; CBDMP, California Birth Defects Monitoring Program.

Table 3

Application of study inclusion/exclusion criteria to define spontaneous very preterm births (VPTBs) and type of specimens available by race-ethnic group, California Very Preterm Birth Study

	White	Hispanic	Black
1. No. of potential cases identified through PNS and NBS linkage	385	385	330
2. Additional VPTBs without newborn specimens, for maternal-only analysis	44	55	43
3. Total number of first eligible VPTBs identified for chart review	428	440	372
4. Total number of confirmed VPTBs	401	369	323
Total excluded[a]	27	71	49
Medical chart not available	15	46	37
Not a singleton birth	6	4	3
Not a livebirth	3	4	2
Not a VPTB	4	19	7
5. Total number of spontaneous VPTB cases	207	217	177
a. With a maternal specimen only	21	30	28
b. With maternal and infant specimens	186	187	149
Total excluded[a]	194	152	146
Pre-eclampsia	95	78	78
Intrauterine growth retardation	46	32	32
Cervical cerclage	26	20	29
Pre-labour C-section due to medical conditions not listed	17	9	14
Other infant birth defects reported in maternal charts[b]	13	16	6
Placenta praevia at delivery	17	8	8
Mullerian anomaly[c]	13	15	2
Pregnancy achieved by assisted reproductive technologies	14	3	2
Sickle cell disease (maternal)	0	0	8
Trauma (with or without placenta abruption	0	2	2
Induction of labour due to medical conditions not listed	0	2	2
Alpha/beta thalassaemia	1	1	0
Diethylstilbestrol (DES) exposure	1	0	0

[a] Numbers in subcategories do not add to the total excluded due to overlapping groups.

[b] Includes cases born in hospitals or time peridos not covered by the California Birth Defects Monitoring Program (CBDMP) registry, non-structural malformations, and two cases missed by the CBDMP registry.

[c] Mullerian anomaly is defined as segmental Mullerian agenesis or hypoplasia, double uterus, unicornuate uterus, uterus didelphys, bicornuate uterus, septate uterus, septate vagina, arcuate uterus and diethylstilbestrol-related anomaly.

PNS, Califonrnia Prenatal Screening programme; NBS, California Newborn Screening programme.

Table 4

Selected characteristics of cases of spontaneous very preterm birth (number and percent) by race-ethnic group, California Very Preterm Birth Study

	White (*n* = 207)	Hispanic (*n* = 217)	Black (*n* = 177)	
Characteristics	***n* (%)[a]**	***n* (%)[a]**	***n* (%)[a]**	***P*[b]**
Type				
Preterm labour	108 (52.2)	119 (54.8)	78 (44.1)	NS
Preterm premature rupture of membranes	98 (47.3)	98 (45.2)	99 (55.9)	
Unknown	1 (0.5)	0 (0.0)	0 (0.0)	
Pre-pregnancy medical conditions[c]				
Pre-pregnancy hypertension	3 (1.5)	1 (0.5)	3 (1.7)	NS
Pre-pregnancy diabetes	1 (0.5)	1 (0.5)	2 (1.1)	NS
Pre-pregnancy body mass index ≥ 30[d]	16 (7.7)	32 (14.8)	41 (23.2)	<0.01
Medical conditions during pregnancy[c]				
Gestational diabetes	11 (5.3)	14 (6.5)	7 (4.0)	NS
Anaemia	20 (9.7)	14 (6.5)	19 (10.7)	NS
Chorioamnionitis	80 (38.8)	99 (45.6)	67 (37.9)	NS
Urinary tract infection	29 (14.1)	39 (18.0)	33 (18.6)	NS
Group B Streptococcus	29 (14.1)	19 (8.8)	30 (17.0)	<0.05
Bacterial vaginosis	6 (2.9)	24 (11.1)	12 (6.8)	<0.01
Chlamydia	0 (0.0)	11 (5.1)	11 (6.2)	<0.01
Trichomoniasis	0 (0.0)	1 (0.5)	3 (1.7)	NS
Gonorrhoea	0 (0.0)	0 (0.0)	1 (0.6)	NS
Source of gestational age				
Ultrasound	152 (73.4)	136 (62.7)	125 (70.6)	NS
LMP with ultrasound confirmation	41 (19.8)	70 (32.3)	41 (23.2)	
LMP without ultrasound confirmation	14 (6.8)	11 (5.1)	11 (6.2)	

[a] Column %.

[b] *P*-value for comparisons between race-ethnic group. NS: *P*>0.05.

[c] The medical conditions before or during pregnancy are not mutually inclusive/exclusive. A woman could have multiple conditions before or during her pregnancy.

[d] kg/m^2.

LMP, last menstrual period.

Table 5

Selected maternal, pregnancy and infant characteristics (%) of spontaneous very preterm birth cases and controls, by race-ethnic group, California Very Preterm Birth Study

	White		Hispanic		Black	
Characteristics	**Cases % (*n* = 207)**	**Controls % (*n* = 200)**	**Cases % (*n* = 217)**	**Controls % (*n* = 253)**	**Cases % (*n* = 177)**	**Controls % (*n* = 343)**
Age (years)						
<20	3.4	1.0	15.2	14.6	19.8	16.9
20–34	76.2	84.0	74.2	75.1	70.0	72.6
35+	20.3	15.0	10.6	10.3	10.2	10.5
Education						
<High school	4.8	3.0	56.7	55.3	26.0	16.9
High school	20.3	20.5	28.1	30.0	31.6	37.0
Some college	24.6	20.0	9.7	9.9	28.8	31.2
College or more	46.9	55.5	4.6	4.4	11.9	10.2
Missing	3.4	1.0	0.9	0.4	1.7	4.7
Parity						
0	66.2	50.0[a]	43.3	32.8	40.7	42.6
1	22.2	25.5	24.4	30.0	26.0	27.1
2+	11.1	19.5	32.3	37.2	33.3	30.3
Missing	0.5	0.0	0.0	0.0	0.0	0.0
Initial month of prenatal care						
First month	45.4	42.0	35.0	28.9	31.1	32.7
Second month	35.8	43.0	44.7	40.7	34.5	36.4
Third month	14.4	10.5	12.4	21.0	21.5	17.8
Fourth month or later	3.4	3.0	6.0	8.6	11.9	11.1
Missing	1.0	1.5	1.8	0.8	1.1	2.0
Gestational age (completed weeks)[b]						
20–25	22.2	0.0	29.0	0.0	30.5	0.0
26–28	26.1	0.0	28.1	0.0	17.5	0.0
29–31	51.7	0.0	42.9	0.0	23.2	0.0
32–33	0.0	0.0	0.0	0.0	28.8	0.0

	White		Hispanic		Black	
Characteristics	**Cases % (*n* = 207)**	**Controls % (*n* = 200)**	**Cases % (*n* = 217)**	**Controls % (*n* = 253)**	**Cases % (*n* = 177)**	**Controls % (*n* = 343)**
37–39	0.0	67.0	0.0	61.7	0.0	66.5
40–41	0.0	33.0	0.0	38.4	0.0	33.5
Birthweight (g)						
<1500	60.9	0.0	70.5	0.0	60.5	0.0
1500–2499	39.1	0.0	29.5	0.0	39.5	0.0
2500–4499	0.0	60.9	0.0	97.6	0.0	99.4
4500+	0.0	60.9	0.0	2.4	0.0	0.6
Male infant	60.9	50.0[a]	55.3	52.2	50.3	52.5

All data from birth certificate with the exception of gestational age.

[a] $P < 0.05$ for comparison between cases and controls.

[b] Gestational age based on best available ultrasound and last menstrual period data from prenatal screening or hospital charts; see *Methods* for details.