Racial/ethnic differences in the monthly variation of preeclampsia incidence
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OBJECTIVE: The purpose of this study was to assess monthly patterns in preeclampsia risk separately by race/ethnicity.

STUDY DESIGN: We conducted a cohort study of 20,794 white women and 18,916 black women who received care at 12 hospitals in the United States.

RESULTS: Among white women, there was a significant U-shaped trend in the incidence of preeclampsia: the incidence was highest in winter months, reached its nadir in mid August, and subsequently increased through the fall months (P < .05). When compared with occurrences in January, the adjusted odds ratios were 0.65 (95% CI, 0.43, 0.99) for May, 0.76 (95% CI, 0.51, 1.13) for June, 0.64 (95% CI, 0.43, 0.97) for July, and 0.64 (95% CI, 0.42, 0.96) for August. Among black women, there was no association between month of delivery and preeclampsia risk (P = .81).

CONCLUSION: Our finding that the incidence of preeclampsia decreases in white women during the summer months and that no pattern exists in black women suggests that, in each subgroup, different or competing environmental exposures may be important for the pathogenesis of preeclampsia.

Key words: month, preeclampsia, pregnancy, race/ethnicity, season

Preeclampsia is a multisystemic, pregnancy-specific disorder that is diagnosed by new-onset hypertension and proteinuria after 20 weeks of gestation. It is a leading cause of morbidity and death among mothers and infants worldwide.1 In developed countries, perinatal mortality rates of infants of preeclamptic mothers is increased 5-fold.2 Nearly 15% of preterm births are medically indicated premature deliveries for preeclampsia,2 and 30% of neonates of preeclamptic pregnancies are growth restricted.3 In the United States, racial/ethnic disparities exist in preeclampsia rates, with preeclampsia more common and severe in black women.4,5 Despite the public health importance of preeclampsia, its cause remains obscure. To provide insight into the potential role of environmental factors in the pathophysiologic condition of preeclampsia, researchers have studied seasonal or monthly changes in its occurrence. Results of past studies have been variable.6-13 This is not surprising, given that the studies were conducted in dissimilar populations, regions of the world, and climates, where environmental exposures may fluctuate greatly. Moreover, even if environmental factors are fairly constant across studies, the same exposure may have a vastly different impact on the pathophysiologic condition of preeclampsia in distinct populations of pregnant women, depending on their underlying characteristics.

Indeed, a limitation of work done in this area is that, in most cases, each study population was relatively homogeneous, which limited the investigators’ ability to examine whether patterns in preeclampsia occurrence were modified by maternal variables. An examination of seasonal or monthly patterns in preeclampsia risk that is stratified by important maternal characteristics, such as race/ethnicity, may provide insight into the pathogenesis of the disorder and aid in our understanding of disparities in preeclampsia outcome.

We had the opportunity to study changes in the incidence of preeclampsia across the year in a large, heterogeneous cohort of pregnant women in the United States who had a rigorous diagnosis of preeclampsia. We sought to study this association in the total population and by race/ethnicity.

Materials and Methods
Data came from the Collaborative Perinatal Project (1958-1964), a prospective study of women attending prenatal care at 12 US hospitals.14 The study centers were Boston, MA; Buffalo, NY; New Orleans, LA; New York–Columbia; Baltimore, MD; Richmond, VA; Minneapolis, MN; New York–Metropolitan; Portland, OR; Philadelphia, PA; Providence, RI; and Memphis, TN. An in-person interview at enrollment collected data on demographic, socioeconomic, and behavioral information. Detailed data were also collected at each prenatal visit, during labor and delivery, and during the postpartum period.

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Of the >55,000 pregnancies that were included in the study, we selected singleton pregnancies from women who identified their race/ethnicity as non-Hispanic white or non-Hispanic black, who gave birth from 20-45 weeks of gestation, and who did not have chronic hypertension or elevated blood pressure at <24 weeks of gestation (n = 43,208). From this sample, we excluded women with missing data on preeclampsia (n = 269) or with covariates in the final model (n = 89). Because we wanted to compare preeclamptic pregnancies with normotensive pregnancies, we also eliminated 3140 women who had transient hypertension of pregnancy (gestational hypertension in the absence of proteinuria). The final analytic sample was 39,710 women.

Blood pressure was measured at entry and at each prenatal visit, during labor and delivery, and after delivery. Korotkoff phase 4 (muffling) or phase 5 (disappearance) was used for diastolic blood pressure. Random urine samples were tested for albumin at each prenatal visit. A validation study in which information on blood pressure and urinary albumin was checked against that in the original medical records showed remarkable accuracy.

Preeclampsia was defined as gestational hypertension and proteinuria and return of abnormalities to normal in the postpartum period. Gestational hypertension was defined as ≥2 measurements of systolic blood pressure of 140-159 mm Hg and/or diastolic blood pressure of 90-109 mm Hg for the first time after 24 weeks of gestation. In the intrapartum period, the first 5 pressure levels that were obtained after hospital admission for delivery were averaged. Proteinuria was defined as 2 random urine dipsticks of 1+ protein or 1 dipstick of 2+ protein.

The date of delivery came from hospital records. Data on maternal age (<20, 20-29, ≥30 years), parity (primiparous, multiparous), marital status (unmarried, married), and smoking status at entry (smoker, nonsmoker) were also available.

### Analysis

Multivariable logistic regression was used to assess the independent association between the timing of delivery and the risk of preeclampsia. First, the delivery date was categorized on the basis of the month of delivery, as in previous studies. A drawback to this method is that it imposes arbitrary cutpoints on the delivery date that may not have biologic relevance and do not make efficient use of within-month information. Therefore, as an alternative, we used spline regression to assess the smoothed association between the timing of delivery and preeclampsia risk. Spline regression more closely approximates nonparametric regression, which makes no assumptions about the exposure-disease relation. We specified the date of delivery as the day of the year (a continuous variable [ie, day 1-365]) and then used methods proposed by Witte and Greenland to determine the most appropriate specification of the delivery day of the year in our model. A restricted quadratic spline with a knot at day 200 was found to have the best fit in the models for the total population (P = .01) and among white women (P < .05). Although odds ratios can be calculated for any day of the year, we chose day 75 (March 16), day 150 (May 30), day 225 (August 13), and day 300 (October 27) as representative values, with day 1 (January 1) as the referent.

We fit parsimonious regression models by fitting full models with potential effect modifiers and confounding variables (maternal age, race/ethnicity, parity, marital status, study site, gestational age at delivery, smoking status, and delivery year). Effect modification on the multiplicative scale by race/ethnicity was assessed by comparing stratum-specific point estimates. Potential confounders were considered not to be influential and were removed from the model if their inclusion did not satisfy our a priori change-in-estimate criterion (a change in the coefficient of >8%). Parity, maternal age, and year of delivery met our definition of confounding and were included in the final models. In all models, standard errors were adjusted for clustering on patient identification number because of repeated pregnancies to the same woman in the dataset. Adjusted odds ratios were used to approximate risk ratios because preeclampsia was rare in our population.

### RESULTS

Approximately 52% of the sample was white and 48% was black. Most women were married (76%) and aged 20-29 years (59%). Approximately 31% of women were primiparous, and roughly one-half of the women were smokers at study entry. Preeclampsia complicated 3.4% of pregnancies.

The prevalence of preeclampsia was highest in January deliveries and lowest in July, August, and September deliveries.
As a function of the day of the year in a population with a large proportion of younger mothers, we observed that preeclampsia was most common in November, December, and January and was least common in summer months. Among white women, the risk of preeclampsia decreased steadily from January 1 to reach its nadir by mid-August and subsequently increased through the rest of the year. Contrary to this clear trend in white women, there was no significant association between timing of delivery and preeclampsia risk among black women.

We are unaware of any published study that assessed racial/ethnic differences in seasonal or monthly patterns of preeclampsia or examined this association in a population with a large proportion of black women who lived in a temp-
The prevalence of preeclampsia by the month of delivery and delivery day of the year by race/ethnicity

The prevalence of preeclampsia by the month of delivery and 95% CI among A, white women (n = 20,794) and B, black women (n = 18,916). Smoothed relationship between the delivery day of the year and the unadjusted prevalence of preeclampsia among C, white women and D, black women. The solid line represents the point estimate; the dotted lines represent 95% confidence bands. The association in white women was quantified with a logistic regression model in which the day of delivery was specified as a restricted quadratic spline with a knot at day 200 (spline coefficients: P < .05). Among black women, there was no association between the delivery day of the year and preeclampsia, regardless of how the variable was specified in the model.

The specific mechanisms underlying the preeclampsia patterns that we and others observed have not been elucidated. Some investigators have suggested that, similar to its effects on acute myocardial infarction, colder ambient temperatures in winter may cause peripheral vasoconstriction that exacerbates a maternal-fetal environment already primed for preeclampsia and may trigger onset of the disease. However, seasonal patterns exist in preeclampsia even in regions where there are no winter temperature extremes. It is possible that, in the temperate climate of the United States, a combination of other variables that are associated with preeclampsia and have seasonal periodicity may be important. Monthly changes in patterns of leisure-time physical activity, dietary intake, acute infections, asthma symptoms, depression and anxiety, and sunlight exposure may predispose women to preeclampsia. We did not have access to such variables in the Collaborative Perinatal Project and could not explore these mechanisms directly.

Our assertion that summertime decreases in the incidence of preeclampsia occur in white women and that no clear pattern exists in black women suggests that, in each subgroup, different or competing environmental exposures may be important for the pathogenesis of preeclampsia. It is also possible that exposures with seasonal periodicity in white populations do not vary seasonally in black women. Unfortunately, there are few data available that describe seasonal patterns in key exposure variables by race/ethnicity. Moreover, little is known about how race/ethnicity modifies the effect of important seasonal exposures on preeclampsia risk or how the pathophysiologic condition of preeclampsia specifically differs by race.

Our study was limited by a lack of ultrasound confirmation of pregnancy dating, which prevented us from studying the incidence of preeclampsia in relation to estimated month of conception. Further, misclassification of gestational age at delivery may have prevented us from fully adjusting for this confounder in our analysis. Additionally, we lacked sufficient data to explore potential mechanisms that might explain the association that we observed. Because this study was conducted in the 1960s, we cannot rule out the possibility that exposures that influenced the monthly patterns in preeclampsia that
REFERENCES


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