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The prevalence of preterm birth and season of conception

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Summary

Preterm birth is a major obstetric problem. An exploration of the season of conception in relation to preterm birth may provide direction in the search for risk factors. We conducted a retrospective cohort study of 82 213 singleton livebirths (20–45 weeks' gestation) to 61 630 women at Magee-Womens Hospital, Pittsburgh, PA, from 1995 to 2005. Conception was estimated based on gestational age determined by best obstetric estimate. Fourier series analysis was used to model seasonal trends.

Spontaneous preterm birth at <37 weeks was associated with conception season ($P < 0.05$). The peak prevalence occurred among conceptions in winter and spring (peaking February 23 at 6.9%), with an average trough among late summer/early autumn conceptions (August 25 at 6.2%). The pattern for spontaneous preterm birth <32 weeks was similar ($P < 0.05$), with the peak on March 13 (1.7%), and nadir on September 12 (1.4%). Results were similar when indicated preterm births were included. These seasonal changes may increase our insight into the role of exposures with seasonal periodicity in the pathophysiology of preterm birth.

Keywords

preterm delivery; season of conception

Introduction

Preterm birth is the most important problem in modern obstetrics. It causes significant infant morbidity and mortality and incurs an estimated annual societal economic burden in excess of \$26.2 billion in the United States.¹ Spontaneous preterm births that occur following spontaneous preterm labour or preterm premature rupture of fetal membranes account for approximately two-thirds of preterm births.^{2,3} Decades of epidemiological and mechanistic research support the notion that spontaneous preterm birth is the clinical consequence of

several possible aetiological pathways.⁴ The ‘syndrome’ of spontaneous preterm birth may occur as a result of the convergence of the influence of a multitude of common, complex exposures.⁴ In this regard, it is thought to be analogous to adult coronary artery disease.⁵

A number of exposures have been implicated as risk factors for spontaneous preterm birth. These include cigarette smoking, maternal underweight, urogenital infections, poor socio-economic status and African-American race.^{4,5} Certainly, our understanding of the environmental contributors to spontaneous preterm birth is incomplete. As has been the case with other common, complex conditions such as coronary artery disease,^{6,7} an exploration of seasonality of disease may provide a direction in the search for risk factors. In an effort to raise hypotheses regarding early pregnancy exposures that may predispose to preterm birth, we sought to determine whether the season of conception bore any relation to subsequent preterm birth. We focused on season of conception based on the notion that the aetiological roots of spontaneous preterm birth lie in the beginning of pregnancy, weeks to months before the clinically recognised events of parturition.

Material and methods

We used data from the Magee Obstetric Medical and Infant database – a database established in 1995 to collect comprehensive maternal, fetal and neonatal outcomes on all women delivering at Magee-Womens Hospital in Pittsburgh, Pennsylvania. Electronic and medical record data on all deliveries were obtained and collated from prenatal records and hospital charts, including delivery records. The database was surveyed periodically to maintain its accuracy by direct comparison at random with patient charts and by examining frequencies for variables that contain data outliers upon download which, once identified, were verified or corrected by means of medical chart review. The existence of personal identifying information in the perinatal database was eliminated to ensure that confidentiality of all patient records was maintained. The University of Pittsburgh Institutional Review Board approved our study.

There were 83 059 singleton deliveries of liveborn infants from 20 to 45 weeks’ gestation at Magee-Womens Hospital from 1 January 1995 to 31 December 2005. We excluded 1% of the sample because of missing data on maternal race/ethnicity ($n = 678$), parity ($n = 11$) or infant birthweight ($n = 157$). The final analytical sample was 82 213 deliveries, which came from 61 630 unique women. A total of 37 502 women had two or more deliveries in the data set.

Gestational age was determined by best obstetric estimate. This estimate was based on the last menstrual period (LMP), supplemented by other evidence such as uterine size, detection of fetal heart sounds and first or second trimester ultrasonography when carried out. Although the database did not indicate how gestational age was specifically determined in each patient, 78% of patients that deliver in the hospital have a dating ultrasound by 20 weeks’ gestation and 92% have an ultrasound before delivery (Magee-Womens Hospital quality assurance data, 2006). We calculated the estimated date of conception based on the date of delivery and gestational age at delivery. Preterm birth was defined as a delivery occurring at 20–36 completed weeks of gestation. We also studied preterm births occurring

at 20–31 completed weeks of gestation. We defined a spontaneous preterm birth as a delivery occurring after preterm labour with intact membranes or preterm pre-labour rupture of the fetal membranes.

In the primary analysis, date of the estimated conception was studied as a continuous variable using Fourier series terms (described below) but, for other analyses, conception date was grouped by month of the year or by season [winter (December, January, February), spring (March, April, May), summer (June, July, August) and autumn (September, October, November)]. Maternal sociodemographic data were based on patient declaration on admitting forms. Maternal race/ ethnicity was self-reported as non-Hispanic white, non-Hispanic black, Hispanic, Asian, Native American or other. We categorised women as white, black or other because only 4% of the population reported a race/ethnicity that was not white or black. Data on marital status (married, unmarried), education (less than high school, high school or equivalent, some college, completed college) and smoking status (smoker, non-smoker) were also available.

Analysis

Seasonal patterns in preterm birth were investigated using Fourier series methods (single cosinor analysis⁸). Fourier series are smooth linear functions with terms roughly orthogonal to each other. They are naturally cyclic in that the smoothed effect continues from December to January. For these reasons, Fourier series are considered to be the natural mathematical models for seasonality. Borrowing previous notation,^{9,10} we employed the first p pairs of terms of the Fourier series: $S(\theta_i, p) = \sum_{r=1}^p \{\beta_r \sin(r\theta_i) + \gamma_r \cos(r\theta_i)\}$ where angle θ_i is the point in the annual cycle that the i^{th} woman's conception occurred. We denoted the number of days between 1 January 1950 and the i^{th} woman's conception as D_i , and calculated this angle in radians: $\theta_i = 2\pi(D_i \bmod 365.25)/365.25$. Therefore, the seasonal effects of conception on the binary outcome preterm birth are modelled by adding $S(\theta_i, p)$ to the linear predictor of a logistic regression model (i.e. β_i and γ_i are parameters in the model). In our data, we found that only the first pair of Fourier terms (F1 model: sine and cosine) was significant based on a likelihood ratio test ($\alpha = 0.10$).

Multivariable logistic regression models were built using generalised estimating equations (GEE) to account for intra-individual correlation of repeated pregnancies among women in the dataset.¹¹ All models were run with and without adjustment for potentially confounding variables defined a priori: maternal age, race/ethnicity, parity, education and marital status. The overall Wald P -value best represents the Fourier model fit^{9,10} and is therefore presented for each model. Finally, we assessed effect modification on the multiplicative scale by race/ethnicity, parity, age, smoking status and education by visually inspecting stratified Fourier seasonality graphs to ensure meaningful differences, and supplemented this with examining Wald P -values of interaction terms in the GEE models.

Results

The majority of women were 30 years old, non-Hispanic white, multiparous, married, college-educated and non-smokers (Table 1). Women with a summer conception were

slightly more likely to be older, non-Hispanic white, college-educated and non-smokers compared with women who conceived in other seasons. There were more births occurring in spring ($n = 21\,202$) and summer ($n = 21\,611$) than in winter ($n = 19\,311$) and autumn ($n = 20\,089$).

Pregnancies that were conceived in the summer and autumn had the lowest prevalence of preterm birth <37 weeks ($P < 0.01$), spontaneous preterm birth <37 weeks ($P < 0.01$), preterm birth <32 weeks ($P < 0.01$) and spontaneous preterm birth at <32 weeks ($P < 0.05$) (Table 2). After adjustment for maternal age, race/ ethnicity, marital status, education and parity, pregnancies with summer and autumn conceptions had 8–19% reductions in risk of subtypes of preterm birth.

The prevalence of preterm birth <37 weeks by month of conception is shown in Fig. 1. The prevalence was highest among conceptions in March and lowest in September. In a logistic regression model fitting the first pair of Fourier series terms, preterm birth at <37 weeks was significantly associated with season of conception ($P < 0.01$). Figure 1 shows the predicted prevalence of preterm birth <37 weeks based on this model. The average peak prevalence occurred among conceptions in early spring (peaking March 13 at 11.5%), with an average trough among early autumn conceptions (September 11 at 10.4%). The seasonal pattern remained significant after adjustment for maternal age, race/ ethnicity, marital status, education and parity ($P < 0.0001$).

When we restricted cases to spontaneous preterm births <32 weeks, a similar significant seasonal pattern was observed (Fig. 1; $P < 0.05$). The predicted prevalence of spontaneous preterm birth <37 weeks was highest among conceptions in late winter (peaking February 23 at 6.9%) and had an average nadir among conceptions in late summer (trough August 25 at 6.2%). Controlling for confounders only slightly attenuated the seasonal effect ($P < 0.0001$).

For preterm birth <32 weeks, March and May conceptions had the highest prevalence, with conceptions in August having the lowest prevalence (Fig. 2). Based on the logistic regression model fitting the first pair of Fourier series terms, preterm birth <32 weeks was significantly related to season of conception (Fig. 2; $P < 0.01$). The average peak prevalence was found among early spring conceptions (peaking at 2.7% on March 17) and had an average nadir among early autumn conceptions (trough at 2.1% on September 16). The seasonal effect remained after controlling for maternal age, race/ethnicity, marital status, education and parity ($P < 0.0001$).

Season of the conception was also significantly associated with the prevalence of spontaneous preterm birth <32 weeks (Fig. 2; $P < 0.05$). The average peak prevalence was among early spring conceptions (highest on March 13 at 1.7%), and had an average nadir among early autumn conceptions (trough on September 12 at 1.4%). The results were not meaningfully affected by adjustment for potential confounders ($P < 0.0001$).

For preterm birth and spontaneous preterm birth at <35 weeks, rates were also highest in late winter/early spring and lowest in summer (data not shown). None of the seasonal effects reported here varied by maternal race/ethnicity, parity, age, smoking status or education.

Discussion

In this very large cohort of deliveries in Pittsburgh, we observed that the prevalence of preterm birth was significantly related to season of estimated conception. The prevalence was lowest when conception occurred in late summer and early autumn, and rose to its peak among conceptions in early spring. This seasonal pattern was consistent for spontaneous preterm births at <37 and <32 weeks' gestation and when studying spontaneous and indicated preterm births combined.

To our knowledge, ours is the first report to study the prevalence of preterm birth in relation to seasonal or monthly patterns of estimated conception. Others examined the frequency of preterm birth related to the month or season of birth, and did not distinguish spontaneous from obstetrically initiated deliveries. In over 482 000 singleton pregnancies delivered in London from 1988 to 2000, Lee and colleagues found that the prevalence of preterm birth (gestational age 26–36 weeks) reached its peak in winter and steadily declined to its nadir in summer.¹² Investigators of two studies conducted in large U.S. populations reported that the lowest probability of preterm birth, defined as gestational age 29–37 weeks¹³ and gestational age 27–35 weeks,¹⁴ occurred among births in spring, and the highest probability was among births occurring in the second half of the year. A bimodal pattern with peaks of preterm birth prevalence occurring in winter and summer was observed in Japan.¹⁵ Rayco-Solon and colleagues studied 1916 births in Gambian villages and found that the incidence of prematurity was lowest in births occurring in February (5%), and peaked in July (17%) and October (14%), which paralleled increases in agricultural labour and malaria infections.¹⁰ In Zimbabwe, birth in the early dry season increased the odds of preterm delivery 2.9-fold [95% CI 1.7, 5.2].¹⁶ The inconsistencies in previous results are not surprising, given that they were conducted in dissimilar populations, regions of the world and climates, where environmental exposures that influence gestational length may fluctuate greatly. Furthermore, previous results are difficult to compare with ours because the timing of delivery does not perfectly correlate with timing of conception. Different definitions of preterm birth further complicate comparisons.

The fluctuation that we noted in the prevalence of preterm births across seasons was relatively small. Our study had the power to detect such differences because we had a large sample size of deliveries over a 10-year period. Importantly, investigators who have studied seasonal patterns in preterm births in industrialised countries have reported seasonal differences of a similar magnitude. For instance, in their study of London deliveries, Lee and colleagues reported that the preterm birth prevalence significantly varied between 6.8% and 5.9% across the year.¹² Given that 'season' reflects multiple, possibly competing risk factors, we expected subtle differences, as has been observed in seasonal trends in myocardial infarction.^{6,7} The patterns that we and others have observed are not intended to alter clinical practice but to provide insights into exposures that may be relevant for the pathophysiology of the outcome.

Indeed, the seasonal pattern in preterm birth that we observed, with highest prevalence among late winter/ early spring conceptions and lowest among late summer/early autumn conceptions, lends itself to several possible explanations. Seasonal variation in respiratory

and gastrointestinal viral infections parallels that seen in our study.^{17–19} Burguete and colleagues noted that early pregnancy infections with adeno-associated viruses were related to spontaneous preterm birth.²⁰ The mechanisms underlying this possible association are unclear but warrant further investigation. Another exposure with seasonal periodicity that parallels that seen in our data is allergy/atopy.^{21,22} The phenomenon of mast cell degranulation promoting myometrial contractility and preterm labour is well-described, and the contribution of a hypersensitivity response to the pathophysiology of preterm birth has been reported.^{4,23–26} Interestingly, neonatal IgE concentrations also vary with season of birth in a pattern similar to that described in our study.²⁷

Other plausible mechanisms relate to the physical environment. Traffic-related air pollution in low socioeconomic status neighborhoods has been linked to preterm birth risk, particularly in winter months.²⁸ Ultraviolet sunlight exposure and maternal vitamin D status may also be relevant. Sunlight is the major contributor to vitamin D status.²⁹ Because of the seasonal variation in ultraviolet light, vitamin D nutritional status is best in summer and autumn and poorest in winter and spring.³⁰ Recent data suggest that vitamin D regulates key target genes associated with implantation and has anti-inflammatory and immunomodulatory effects.^{31–33} Therefore, it may contribute to the pathophysiology of preterm birth.

Maternal life style and psychosocial factors with seasonal periodicity,³⁴ such as smoking habits,³⁵ nutritional status,^{36–38} leisure-time physical activity,^{39,40} drug use,⁴¹ and depression and anxiety,^{42,43} which are associated with risk of preterm birth may also contribute to the effect we observed. Unfortunately, we lacked sufficient information to explore potential mechanisms explaining the seasonal patterns that we observed.

It is also possible that the seasonal changes in preterm birth prevalence that we noted are spurious. As observed by Basso *et al.*,⁴⁴ there is a seasonal variation in pregnancy planning. The most fecund couples will achieve pregnancy within their desired season, while the less fecund couples will be more likely to conceive outside of the preferred time period. If low fecundity is a risk factor for preterm birth (which has been noted in some^{45,46} but not all⁴⁷ studies), then the high-risk pregnancies will be unevenly distributed throughout the year. While this confounding bias cannot be controlled, its impact is likely to be small.⁴⁴ A similar bias may occur if women who lost their previous pregnancy attempt to conceive more quickly after their loss and outside of their preferred season. Nevertheless, we observed similar seasonal patterns in preterm birth among both primiparous and multiparous women (data not shown).

In our delivery database, gestational age was based on best obstetric estimate. However, we did not know precisely which patients' gestational ages were determined solely by date of LMP. LMP-derived gestational age is error-prone because mothers may not perfectly recall their LMP and may misinterpret the LMP owing to post-conception bleeding, delayed ovulation or intervening early miscarriage. Nevertheless, gestational age derived exclusively from the LMP was less likely in our dataset, as 78% of women who present for delivery in our hospital have had an ultrasound for dating at <20 weeks' gestation, and 92% of women have an ultrasound before delivery (Magee-Womens Hospital quality assurance data, 2006). As with any large delivery database, misclassification of preterm birth was possible.

However, as the gestational age cut-point for preterm birth is lowered, misclassification is less likely. We observed a significant effect of season of conception with both earlier and later cut-points. It is possible that some births at 20 weeks' gestation (our lower cut-point for inclusion into the study), some stillbirths and miscarriages were misclassified as live-births. However, our database staff classifies deliveries with 1-min Apgar scores of 0 as stillbirths to reduce this misclassification. We lacked reliable data on history of prior preterm birth to explore whether seasonal patterns differed in this high-risk group.

Because approximately 70% of deliveries in Pittsburgh occur at Magee-Womens Hospital, our study had high generalisability for women in our region. Moreover, our examination of preterm birth in relation to season of conception is novel and relevant because the aetiology of preterm birth probably involves exposures that occur long before clinically recognised events.

These epidemiological data support mechanistic research exploring the contribution of exposures with seasonal periodicity such as viral infections, allergies, sunlight and life style variables to spontaneous preterm birth risk. Further investigation into the specific biological mechanism(s) for this finding could aid in efforts aimed at preventing preterm birth.

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Figure 1.

Fitted seasonality of conception model for preterm birth <37 weeks gestation (panel A) and spontaneous preterm birth <37 weeks gestation (panel B). The models fitted to Fourier series used the first pair of Fourier terms (F1 model). The dashed line represents the proportion of preterm birth <37 weeks conceived per calendar month. The solid line represents the Fourier fit for the seasonality of conception of preterm births.

Figure 2.

Fitted seasonality of conception model for preterm birth <32 weeks' gestation (panel A) and spontaneous preterm birth <32 weeks' gestation (panel B). The models fitted to Fourier series used the first pair of Fourier terms (F1 model). The dashed line represents the proportion of preterm birth <32 weeks conceived per calendar month. The solid line represents the Fourier fit for the seasonality of conception of preterm births.

Table 1

Characteristics of 82 213 deliveries at Magee-Womens Hospital (1995–2005): column %

	Total population All <i>n</i> = 82 213	Stratified by season of conception			
		Winter <i>n</i> = 19 740	Spring <i>n</i> = 20 025	Summer <i>n</i> = 21 073	Autumn <i>n</i> = 21 375
Maternal age (years)					
<20	6.9	7.1	7.4	6.4	6.9
20–29	41.3	41.6	41.8	40.3	41.5
30+	51.8	51.3	50.8	53.3	51.6
Maternal race/ethnicity					
Non-Hispanic white	79.3	79.1	77.8	80.3	79.7
Non-Hispanic black	16.8	16.8	18.1	16.1	16.5
Other	3.9	4.1	4.1	3.6	3.8
Parity					
Primiparous	43.6	44.0	44.0	43.3	43.1
Muciparous	56.4	56.0	56.0	56.7	56.9
Marital status					
Married	33.4	32.9	35.0	32.2	33.4
Unmarried	66.6	67.1	65.0	67.8	66.6
Education level					
Less than high school	7.8	7.8	8.4	7.3	7.8
High school or equivalent	29.0	29.5	27.1	28.1	31.2
Some college	21.0	21.0	21.8	21.4	20.8
Completed college	42.0	41.7	42.7	43.2	40.2
Smoking status at delivery ^a					
Non-smoker	83.3	82.3	81.5	85.5	83.6
Smoker	16.7	17.7	18.5	14.5	16.4

^aSmoking data limited to *n* = 67 815.

Table 2

Association between season of conception and preterm birth (*n* = 82 213)

	Preterm birth <37 weeks			Spontaneous preterm birth <37 weeks			Preterm birth <32 weeks			Spontaneous preterm birth <32 weeks		
	Prevalence	Adjusted ^a risk ratio [95% CI]	Adjusted ^a risk ratio [95% CI]	Prevalence	Adjusted ^a risk ratio [95% CI]	Adjusted ^a risk ratio [95% CI]	Prevalence	Adjusted ^a risk ratio [95% CI]	Adjusted ^a risk ratio [95% CI]	Prevalence	Adjusted ^a risk ratio [95% CI]	Adjusted ^a risk ratio [95% CI]
Winter	11.0	0.97 [0.91, 1.03]		6.5	0.92 [0.85, 0.99]		2.4	0.91 [0.79, 1.03]		1.5	0.87 [0.74, 1.03]	
Spring	11.3	1.00 Reference		6.9	1.00 Reference		2.6	1.00 Reference		1.7	1.00 Reference	
Summer	10.3	0.92 [0.86, 0.98]		6.0	0.87 [0.80, 0.94]		2.2	0.84 [0.73, 0.96]		1.4	0.83 [0.70, 0.98]	
Autumn	10.3	0.91 [0.85, 0.96]		6.3	0.91 [0.84, 0.98]		2.1	0.81 [0.71, 0.92]		1.4	0.82 [0.69, 0.96]	

^a Adjusted for maternal age, race/ethnicity, marital status, education and parity.