
Seasonal variation in the incidence of cleft lip and palate based on the age of conception

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Background: The purpose of this study is to identify seasonal changes in the incidence of Cleft lip and Palate (CL/P) in our population.

Methods: All cases of isolated CL/P born in Puerto Rico from January 1998 through December 2002 were identified through the Puerto Rican birth defect registry. Conception dates were estimated based on the reported last menstrual period. All deliveries during this same period were recorded and their conception dates estimated in the same manner. The data was separated into 4 groups for each year studied corresponding approximately to the four seasons.

Results: 484 cases of CL/P were identified among 308,968 live births (incidence 1.57/1000 live births. The lowest incidence of CL/P was seen during fall and winter (1.24 and 1.38/1000 live births respectively) and the

highest during spring and summer (1.77 and 1.97/1000 live births respectively) ($p = 0.002$). The seasons with the highest incidence correspond to the period when the least number of conceptions are occurring. Estimation of relative risks using winter as a reference point (relative risk of 1.0) showed a decrease in the risk of CL/P in fall to .89 (95th confidence interval 0.88 – 1.57), an increase in the risk to 1.28 (CI 1.16 – 2.03) during spring and 1.42 (CI 1.16- - 2.03) during summer.

Conclusions: The reported seasonal variation in incidence may be secondary to the action of yet to be identified teratogens acting on the population at large, or more likely, changes in activity and diet patterns of the population.

Key words: Cleft lip, Cleft palate, Conception, Seasonal variation

Cleft lip results from complete or partial failure of fusion of the maxillary prominence with the medial nasal prominence on one or both sides. Cleft palate results from failure of fusion of the palatine shelves. These are the most common major anomalies of the fetal face detected at birth and are associated to many long-term complications. The incidence of cleft lip/palate varies from 0.7 to 1.4/1000 live births among different populations (1-4). Due to their high correlation with lethal chromosomal anomalies, many of which are lost early in pregnancy, its frequency is much higher during the first trimester than at birth. Although associated to over 100 syndromes and being a typical finding in aneuploidy (especially trisomy 13), at least half of the cases are isolated (5).

The pathophysiologic mechanisms that produce a cleft lip and palate are uncertain. Experiments in rats have identified multiple teratogenic substances such as retinoic acid and some refinery oils as possible etiologic factors (6,7). But in the vast majority of cases, factors contributing to this congenital anomaly remain largely unknown.

One of the first steps in evaluating the possibility of teratogenic influences operating in a population would be to identify if any variations in the incidence of the condition exists throughout the year. Estimation of the time of conception rather than birth date is crucial since it is during the first trimester that most teratogens exert their influences.

The purpose of this study is to identify seasonal changes in the incidence of cleft lip/palate in our population based on estimated conception dates.

Methods

All cases of isolated cleft lip or cleft lip and palate born in Puerto Rico from January 1998 through December 2002 were identified through the Puerto Rican birth defect registry. Institutional Review Board approval was obtained following FDA and OHRP guidelines. Conception dates were estimated based on the reported last menstrual period for each of these pregnancies. Conceptions were assumed to occur 14 days after the first day of the last reported menstrual period. All deliveries during this same period of time were also recorded and their conception dates estimated in the same manner. The data was separated into 4 groups for each year studied corresponding approximately to the four seasons, winter (from January

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1st through March 30th), spring (April 1st through June 30th), summer (July 1st through September 30th) and fall (October 1st through December 31st).

The incidence of cleft lip/palate per 1000 conceptions resulting in live births was calculated for each season based on this data. Statistical analysis of incidence and relative risks was done using a STATA analytical package.

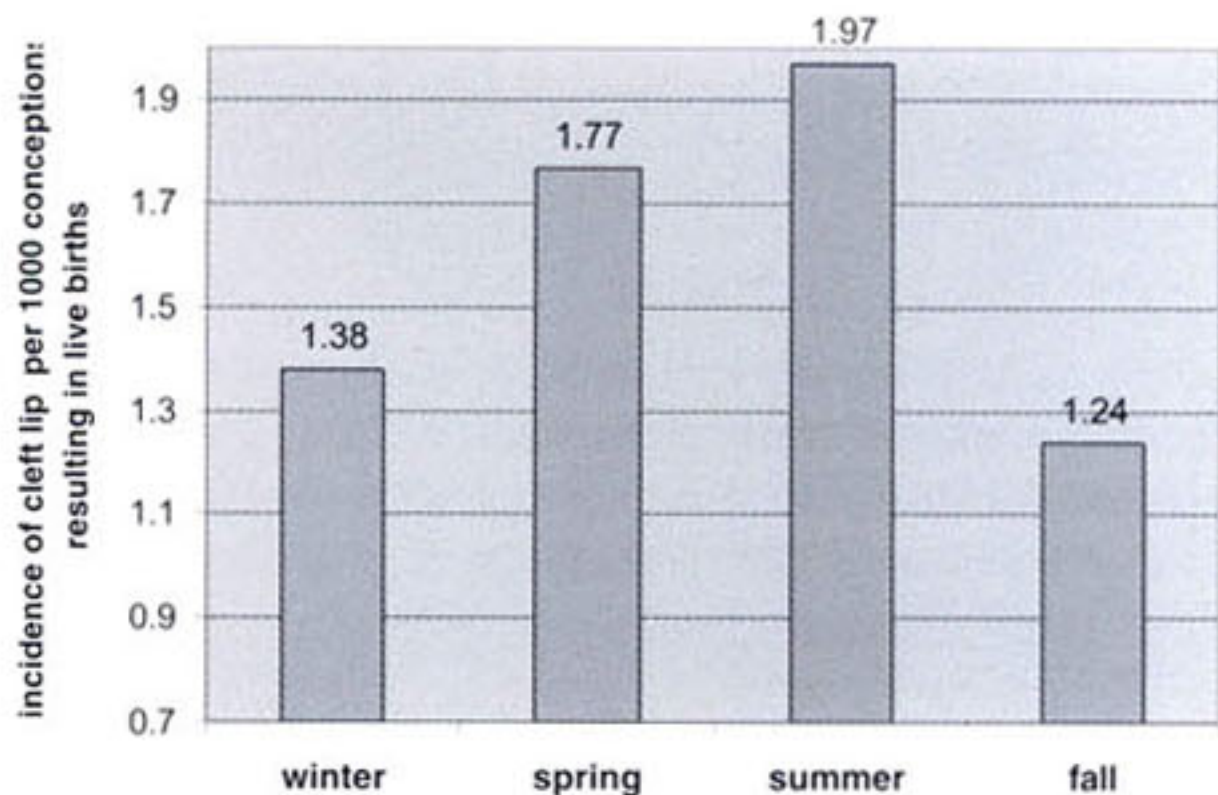
Isolated cleft lip without cleft palate was not analyzed independently and no differentiation was done between unilateral and bilateral cleft lips. The presence of other associated congenital anomalies or syndromes was not considered as part of the analysis.

Results

From 1998 through 2002 there were a total of 484 reported cases of cleft lip/palate among 308,968 live births in Puerto Rico (incidence 1.57/1000 live births or 1 cleft lip per 638 live births). The time of conception was estimated for each of these births and separated into 4 time periods corresponding approximately to the seasons (spring through winter). The conception date of all recorded live births during this time period was also estimated in the

same manner. The results of each seasonal incidence are shown in Figure 1. The lowest incidence of cleft lip/palate was seen during fall and winter (1.24 and 1.38/1000 live births respectively) and the highest during spring and summer (1.77 and 1.97/1000 live births respectively). These differences were significant (p = 0.002). The seasons with the highest incidence of cleft lip/palate correspond to the time period when the least number of conceptions are occurring in Puerto Rico (Figure 2). A 17.2% increase in conceptions occurs during fall and winter as compared to spring and summer. Analysis of each individual year studied showed the same tendency towards higher incidences of cleft lip/palate in spring and summer although the numbers did not reach statistical significance. Estimation of relative risks using winter as a reference point (relative risk of 1.0) showed a decrease in the relative risk of cleft lip/palate in fall to .89 (95th confidence interval 0.88 – 1.57) and an increase in the relative risk to 1.28 (CI 1.16 – 2.03) during spring and 1.42 (CI 1.16 - - 2.03) during summer (Table 1).

Graph 2
Seasonal Variations in the Incidence of Cleft Lip/Palate in Puerto Rico 1998-2002
(484 cases among 308,968 conceptions resulting in live births)



Graph 1
Seasonal variation in the incidence Conceptions resulting in live births in Puerto Rico (1998-2002)
N=308,968

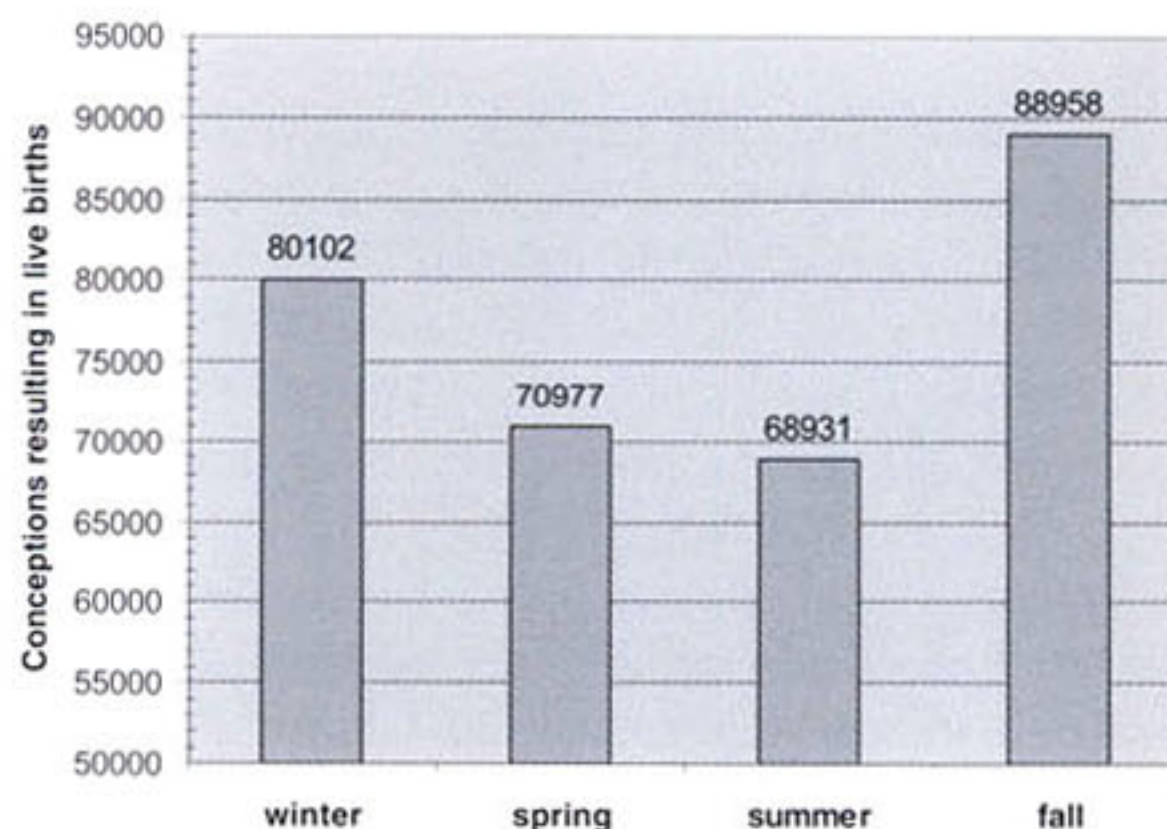


Table 1. Seasonal Variations in the Incidence of Cleft Lip/palate from 1998-2002 in Puerto Rico

Season	Conceptions resulting in live births	Cleft lips/palate	Incidence/ 1000 live births	Relative Risk	[95% confidence interval]	P-value
Spring	70977	126	1.77	1.28	1.17-2.03	0.002
Summer	68931	136	1.97	1.42	1.16-2.03	0.002
Fall	88958	111	1.24	0.89	0.88-1.57	0.259
Winter	80102	111	1.38	1 (ref.)		
Total	308968	484	1.57			

Discussion

Cleft lip and palate are the most common congenital malformations of the head and neck identified at birth. They may occur as an isolated finding or may be related to other structural malformations and syndromes. The incidence of this malformation is estimated to be between 0.7 and 1.4 cases/1000 births (1-4). Our data shows an incidence of 1.57 cases/1000 live births or 1/638 live births, higher than most reports from other countries.

The etiology of these birth defects is uncertain, however, genetic as well as environmental factors are felt to play a role (8-10). Pre-conceptual and first month of pregnancy use of folic acid has been reported to be associated with a 25-50% reduction in the incidence of cleft lip palate (11,12). Other investigators have not found any correlation between vitamin use, smoking, drug use, or urinary tract infections (13). Thus, the exact role of environmental agents and teratogens in the development of this anomaly is far from known.

Conditions that are influenced by the presence of environmental teratogens may show seasonal patterns of occurrence. In order to analyze this possibility, we calculated the dates of conception for our population for all cases of cleft lip/palate and compared them to those of all live births in the island. We have identified a seasonal variation in the incidence of cleft lip and palate in Puerto Rico with the highest rate among conceptions occurring in spring (April through June) and the lowest among conceptions in the fall (October through December). Using winter as a reference point (relative risk of 1), the relative risk of cleft lip/palate during spring is 1.77. This difference is significant ($p=0.002$). The increase in the incidence of this anomaly occurs at the time when the lowest numbers of conceptions are occurring throughout the year. Other investigators have not found these fluctuations (14,15).

Puerto Rico is a Caribbean island of 4 million inhabitants, mostly Hispanics. There are minimal changes in average temperatures and rainfall from one season to another. In spite of this fact, significant differences in conception rates occur through out the year with a 17.2% increase during fall and winter as compared to spring and summer. It is difficult to identify any environmental agent that could play a role in the seasonal changes we have reported. However, patterns of activity, exercise, and food intake appear to change during the course of year in both northern and tropical countries (16,17). Thus, investigation as to the potential effect of teratogens must take these factors into account. In spite of intensive efforts for the last 5 years by the Puerto Rico birth defect prevention campaign to educate the public on the importance of pre-conceptual use of folic acid in preventing birth defects,

less than 32% of pregnant women refer using it prior to pregnancy. This is not surprising when considering that 65% of pregnancies in this population are unplanned, however, even among patients who state that their pregnancy was planned, only 54.6% report use of pre-conceptual folic acid (18). Thus, intake of this and other micronutrients depends largely on their diets.

Studies from our population have identified a greater incidence of mutations in the genes associated to folate metabolism among patients with isolated neural tube defects (19). These patients are believed to need higher intake of folate to overcome this problem in order to prevent the occurrence of birth defects. If the development of cleft lip and palate are influenced by these, or similar, gene defects, seasonal dietary fluctuations may produce transient, folate deficiencies among susceptible individuals.

Our next challenge will be to determine if preventive measures can be established effectively that could avoid the development of these abnormalities. We believe that this data merits further and more detailed research with larger populations.

Resumen

Propósito: Identificar los cambios en la incidencia de labio leporino y paladar hendido (LL/PH) en nuestra población a lo largo del año.

Métodos: Todos los casos aislados de LL/PH nacidos en Puerto Rico entre Enero de 1998 y Diciembre del 2002 fueron identificados através del sistema de vigilancia de defectos congénitos de Puerto Rico. Las fechas de concepción fueron estimadas para cada uno de estos basados en la última regla reportada. Todos los partos durante este mismo período de tiempo fueron registrados y sus fechas de concepción estimadas de la misma manera. Los datos fueron separados en 4 grupos para cada año estudiado correspondiendo a las estaciones del año.

Resultados: 484 casos de LL/PH fueron identificados entre 308,968 nacidos vivos (incidencia 1.57/1000 nacidos vivos). La menor incidencia se notó durante las concepciones de otoño e invierno (1.24 y 1.38/1000 nacidos vivos respectivamente) y las más altas durante primavera y verano (1.77 y 1.97/1000 nacidos vivos respectivamente) ($p = 0.002$). Las estaciones con la mayor incidencia corresponden al período durante el cual el menor número de concepciones esta ocurriendo. El estimado de riesgo relativo (RR) usando invierno como punto de referencia (RR de 1.0) demostró una reducción en RR durante otoño a .89 (95% intervalo de confianza 0.88 – 1.57), y un aumento en riesgo a 1.28 (IC 1.16 – 2.03) durante primavera y 1.42 (IC 1.16- - 2.03) durante el verano

Conclusiones: Las variaciones reportadas durante el año en la incidencia de LL/PH pueden ser secundarias a la acción de teratógenos aún no identificados actuando sobre la población en general o, más probablemente, cambios en la actividad y patrones dietéticos de la población.

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