Seasonal Variations in the Incidence of some Congenital Anomalies in Puerto Rico based on the Timing of Conception

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Background: **Birth defects represent one of the main causes of infant mortality and morbidity around the world.**

***Objective*: The purpose of this study is to identify seasonal changes in the incidence of various congenital anomalies in our population.**

***Methods*: We identified all cases of open neural tube defects, cardiac anomalies, cleft lip and palate and gastroschisis of children born in Puerto Rico and reported to the Health's Department Birth Registry Program between January 1995 and December 2005. The conception dates were determined by estimation 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 for each anomaly was separated into 4 groups for each year studied corresponding to the four seasons. The sample was stratified based on the type of anomaly detected and the season when conception took place.**

***Results*: There is a seasonal pattern in the rate of conceptions in Puerto Rico with the highest incidence during the winter and lowest during the summer months. We detected a statistically significant increase in the incidence and relative risk during the summer months (using winter as a reference) of conceiving a child with open neural tube defects (1.03/1000, RR:1.33), cardiac anomalies (5.22/1000, RR:1.39), or cleft lip and palate (1.68/1000, RR:1.89). Gastroschisis did not show a statistically significant difference in the rate of conceptions, but there was a tendency towards a higher incidence during spring (0.39/1000, RR:1.67).**

***Conclusions*: The reported seasonal variation in the incidence of open neural tube defects, cardiac anomalies, and cleft lip and palate may be secondary to the effect of yet to be identified teratogens acting on the population at large, or, more likely, to changes in activity and dietary patterns of the population.**

Key words: Cleft lip, Cleft palate, Cardiac anomalies, Open neural tube defects, Gastroschisis, Conception, Seasonal variation

Birth defects represent one of the main causes of infant mortality and morbidity around the world, especially in developed countries such as the United States. They occur in approximately 2 to 3 percent of all live births (1). Thus, identification of factors that could reduce the incidence of these conditions is of utmost importance in an attempt to reduce perinatal morbidity and mortality. Although some congenital anomalies have a strong genetic component, in most, the etiology is either unknown or secondary to multiple factors that may affect the developing embryo or may increase its vulnerability to other teratogenic insults.

Some teratogens such as drugs and alcohol are well documented, but others may be exerting their harmful effect without knowledge from the mother. Hyperthermia associated to high fever, for example, has been linked to a higher incidence of congenital anomalies (2). Avoidance of these potentially modifiable risk factors may reduce the incidence of certain congenital anomalies.

We propose that there is an association between unidentified environmental teratogens and the incidence of congenital anomalies. The presence of these environmental teratogens is expected to produce a seasonal variation in exposure and this would be reflected on its effect on the incidence of congenital anomalies throughout the year. The first step in identification of such harmful agents would be to prove that a seasonal variation in the incidence of congenital anomalies exists in our island. If this occurs, it would be reflected in the incidence per conceptions rather than live births. We have published that there were seasonal changes in the incidence of cleft lip and palate based on the age of conception in Puerto Rico between 1998 and 2002 (3), a fact that strongly supports our theory of variable seasonal exposure to teratogens. The purpose of this study is to extend our investigation to other anomalies whose occurrence may also be influenced by environmental factors, mainly congenital cardiac disease, gastroschisis and open neural tube defects, and to evaluate

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if the seasonality of cleft lip and palate persists beyond the years previously studied.

Methods

This is a descriptive retrospective study. All cases of gastroschisis, congenital heart disease, cleft lip and palate and open neural tube defects in children born in Puerto Rico during the study period and identified by the Puerto Rico Department of Health's Birth Defects Registry were included. Those born premature, stillborn, or whose pregnancies are terminated are included in this registry. The study period included from January 1995 through December 2005 for cases of open neural tube defects; January 1999 through December 2005 for cases of cleft lip and palate; January 2001 through December 2005 for gastroschisis; and January 2003 through December 2005 for cases of congenital heart disease. The differences in the study years for each anomaly correspond to the time when surveillance was initiated for these conditions by the Birth Defects Registry. All information obtained was retrospective and anonymous, and, thus, not subject to institutional review board approval based on FDA and OHRP guidelines.

Conception dates were determined using the reported last menstrual period for each of these pregnancies. Conceptions were estimated to have occurred 14 days after the first day of the reported last menstrual period. All deliveries occurring in Puerto Rico during the same period of time were also recorded and their conception dates estimated in the same manner. The data for each anomaly was separated into four groups for each year studied approximately corresponding to the four seasons, winter (January 1rst through March 31st), spring (April 1st through June 30th), summer (July 1st through September 30th) and fall (October 1st through December 31st).

The incidence rates (per 1000 conceptions resulting in live births) of each condition (open neural tube defects, cleft lip and palate, cardiac anomalies, and gastroschisis) was calculated for each season (spring, summer, autumn, and winter). Based on these rates, the relative risks (RR) were estimated with their 95% confidence intervals to determine relative differences in their incidence by season. The reference group in the RR estimation was winter since this is the time when most conceptions tend to occur. Data were analyzed using SAS version 8 (SAS institute Inc., Cay, N.C.).

Differentiation between the different anomalies for each category studied (for example, myelomeningocele versus anencephaly) was not performed and the presence of other concurrent congenital anomalies that could be present was not considered as part of the analysis.

Results

A seasonal variation in the incidence of conceptions resulting in live births was identified to occur in Puerto Rico between 1998 through 2005, with the least conceptions occurring in summer and the greater number occurring in winter (Figure 1). The results for each anomaly studied are reported individually and summarized in Tables 1 to 4.

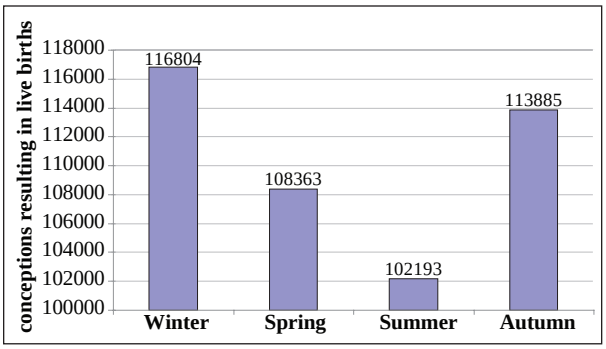

Figure 1. Seasonal Variations in the Incidence of Conceptions Resulting in Live Births in Puerto Rico (1995-2005) (N=441,245)

Cardiac Anomalies (Table 1):

There were a total of 569 cases of congenital heart disease among 152,729 conceptions resulting in live births between January 2003 and December 2005. The incidence per 1000 conceptions resulting in live births varied depending on the season with a peak incidence during the summer months (5.22) and lowest during the fall (2.39). An analysis of the relative risk shows that there is a significantly higher risk of conceiving a child born with congenital heart disease during the summer months as compared to the winter months (relative risk of 1.39, with a 95% confidence interval of 1.12-1.72) and significantly lower risk during the fall (relative risk of 0.64 with a 95% confidence interval of 0.49-0.83).

Table 1. Seasonal Variations in the Incidence of Cardiac anomalies in Puerto Rico from 2003 through 2005

Season	Conceptions resulting in live Births	Cardiac anomalies	Incidence/ 1000 live births	Relative Risk	95% confidence interval
Winter	40264	151	3.75	1(ref.)	
Spring	37410	138	3.69	0.98	0.78-1.23
Summer	35430	185	5.22	1.39	1.12-1.72
Autumn	39625	95	2.39	0.64	0.49-0.83
Total	152729	569	3.72		

Cleft lip and Palate (Table 2):

There were a total of 461 cases of cleft lip and palate in Puerto Rico from January 1999 through December 2005 among 380,727 conceptions. The incidence per 1000 conceptions resulting in live births peaked during the summer (1.68) and was lowest during the winter (0.89). An analysis of the relative risk shows that there is a significantly higher risk of conceiving a child born with a clef lip and palate during all seasons as compared to winter with summer being the highest (relative risk of 1.89 with a 95% confidence interval of 1.46-2.46).

Table 2. Seasonal Variations in the Incidence of Cleft Lip and Palate in Puerto Rico from 1999 through 2005

Season	Conceptions resulting in live Births	Cases of Cleft Lip/Palate	Incidence/ 1000 live births	Relative Risk	95% confidence interval
Winter	101114	90	0.89	1(ref.)	
Spring	93133	108	1.16	1.30	0.99-1.72
Summer	87904	148	1.68	1.89	1.46-2.46
Autumn	98576	115	1.17	1.31	1.0-1.73
Total	380727	461	1.21		

Open Neural Tube Defects (Table 3):

There were a total of 377 cases of open neural tube defects in Puerto Rico from January 1995 through December 2005 among 441,245 conceptions. The incidence was highest during the summer (1.03). The relative risk of conceiving a child with an open neural tube defect only increased significantly during the summer months (relative risk of 1.33 with a 95% confidence interval of 1.01-1.76).

Table 3. Seasonal Variations in the Incidence of Open Neural Tube Defects in Puerto Rico from 1995 through 2005

Season	Conceptions resulting in live Births	Cases of Open Neural Tube Defects	Incidence/ 1000 live births	Relative Risk	95% confidence interval
Winter	101114	90	0.89	1(ref.)	
Spring	93133	108	1.16	1.30	0.99-1.72
Summer	87904	148	1.68	1.89	1.46-2.46
Autumn	98576	115	1.17	1.31	1.0-1.73
Total	380727	461	1.21		

Gastroschisis (Table 4):

There were a total of 83 cases of gastroschisis between January 2001 and December 2005 among 261,583 conceptions resulting in live births. The incidence of this condition showed variation during the seasons with the peak occurring in spring (0.36) and least during the winter (0.23), but an analysis of the relative risk showed that these differences were not significant.

Table 4. Seasonal Variations in the Incidence of Gastroschisis in Puerto Rico from 2001 through 2005

Season	Conceptions resulting in live Births	Cases of Gastroschisis Lip/Palate	Incidence/ 1000 live births	Relative Risk	95% confidence interval
Winter	68887	16	0.23	1(ref.)	
Spring	64339	25	0.39	1.67	0.89-3.13
Summer	60822	22	0.36	1.55	0.81-2.96
Autumn	67535	20	0.30	1.28	0.66-2.46
Total	261583	83	0.32		

Discussion

As our data shows, there is a seasonal variation in the incidence of conceptions resulting in live births in Puerto Rico with the greater number of conceptions occurring during the winter months and the lowest during summer. Many countries, especially those that have large differences in temperature during the year, exhibit a variable pattern in conception rates. However, the difference is higher in Puerto Rico with an observed change in the rate of conceptions of 12.5% between winter and summer. The reason for this phenomenon is not clear since Puerto Rico is a tropical island with small differences in temperature and climate during the year. However, alcohol consumption increases dramatically in Puerto Rico during the winter, and social activities are very frequent during this time increasing the possibility of sexual contacts between individuals that may be intoxicated and thus, less likely to use contraception. The fact that over 60% of pregnancies in Puerto Rico are unplanned supports this possibility (4). This data in itself is important since this may also be reflected in higher rates of sexually transmitted infections. Efforts should be increased during this time of the year to enhance contraception awareness.

We have found a significant difference in the incidence of three of the four congenital anomalies studied (open neural tube defects, cleft lip and palate and cardiac anomalies) in Puerto Rico during the year. The fact that there is a higher possibility of conceiving a child with one of these anomalies during the months when the lowest incidence of conceptions occur is significant in itself. Conditions that are influenced by the presence of environmental teratogens may show seasonal patterns of occurrence depending on the exposure to these teratogens.

Our data supports this possibility. It is difficult to identify any environmental agent that could play a role in these differences. However, patterns of activity, exercise, and diet change during the course of the year in both northern and tropical countries (5-6). An investigation as to the potential effects of teratogens must take these factors into account. In Puerto Rico, the winter months are associated to a higher consumption of what's termed a "traditional" diet with increased intake of grains that may be richer in nutrients such as folic acid. We have previously reported a low pre-conceptional use of folic acid supplements in our population with only 31.5% of patients reporting its ingestion prior to conception (7). Thus, for most patients in P.R., intake of micronutrients depends entirely on their diet which may be richer in them during the winter. Studies in our population have identified a greater incidence of mutations in the genes associated to folate metabolism among patients with isolated open neural tube defects (8). These patients are believed to need higher intake of folate to overcome this problem in order to prevent the occurrence of birth defects. The incidence of cleft lip and palate has also been shown to decrease with pre-conceptional and first-month use of folic acid (9-10). This further supports our hypothesis that fluctuations in diet may be associated to these seasonal variations.

Other possible etiologies may play a role. Both, physical activity as well as climate temperature increase during summer months. This may be associated to a greater propensity for development of congenital anomalies (11). In addition, we can't rule out the presence of unknown teratogens that may exert their damaging effects with a seasonal pattern during the year.

Although the differences were not statistically significant, there was an increase in the incidence of gastroschisis among conceptions that occurred during the spring months. Gastroschisis is considered an intra-uterine vascular accident in which one of the branches of the omphalo-mesenteric artery is occluded resulting in failure of complete closure of the ventral wall. The use of ibuprofen and Neo-Synephrine has been linked to a higher incidence of this condition (12). Since there is an increase in the incidence of allergic diseases during spring, consumption of these products may also increase. Greater efforts should be made at warning patients regarding the risk associated to these medications.

The above data merits further studies, especially those concerning changes in micronutrient intake during the year that could affect the incidence of cardiac anomalies, open neural tube defects, and cleft lip and palate among our patients. Our continuing challenge is to determine if effective preventive measures could be established to avoid or reduce the incidence of these conditions in our island.

Resumen

Identificar cambios estacionales en la incidencia de varias anomalías congénitas en nuestra población. Todos los casos de defectos de tubo neural, anomalías cardiacas, labio y paladar fisurado y gastrosquisis en niños nacidos en Puerto Rico e informados al Registro de Anomalías Congénitas del Departamento de Salud entre enero 1995 y diciembre 2005 fueron identificados. Las fechas de concepción fueron estimadas basándose en la fecha del último período menstrual informado. Todos los nacimientos vivos durante este mismo periodo de tiempo fueron evaluados y sus fechas de concepción calculadas de la misma manera. Los datos para cada categoría de anomalías fueron separados en 4 grupos por cada año estudiado correspondiendo a las 4 estaciones. Hay un patrón estacional en la tasa de concepciones en Puerto Rico y la mayor incidencia ocurre durante el invierno y la menor durante los meses de verano. Identificamos un aumento en la incidencia y el riesgo relativo (usando el invierno como referencia) de concebir un niño con defectos del tubo neural (1.03/1000, RR: 1.89), cardiopatías (5.22/1000, RR: 1.39) y labio/paladar fisurado (1.68/1000, RR: 1.89) durante los meses de verano. Estas diferencias son estadísticamente significativas. La gastrosquisis no demostró una diferencia significativa desde el punto de vista estadístico en la incidencia de concepciones, pero se notó una tendencia a una mayor incidencia durante la primavera (0.39/1000, RR:1.67). La variación estacional informada en cuanto a la incidencia y al riesgo relativo de defectos del tubo neural, cardiopatías y labio/paladar fisurado puede ser secundaria al efecto de teratógenos aún no identificados que actúan en la población general. Pero es más probable que dependa de cambios en la actividad y los patrones dietéticos de nuestra población.

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