Increasing Prevalence of Gastroschisis: Population-based Study in California

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Objective To evaluate time trend of gastroschisis and examine the epidemiological risk factors for gastroschisis.

Study design This population-based study analyzed the active surveillance data from the California Birth Defects Monitoring Program from 1987 to 2003.

Results The overall birth prevalence of gastroschisis was 2.6 cases per 10,000 births (908 cases in >3.5 million births). In the adjusted analysis, by using the age of 25 to 29 years as the reference, mothers aged 12 to 15 years had a 4.2-times greater birth prevalence (95% CI, 2.5-7.0), and fathers aged 16 to 19 years and 20 to 24 years had 1.6- and 1.5-times greater birth prevalence (95% CI, 1.1-2.1 and 1.2-1.8), respectively. Compared with non-Hispanic whites and US-born Hispanic, both foreign-born Hispanics and blacks had adjusted prevalence ratio of 0.6 (95% CI, 0.5-0.7 and 0.4-0.9, respectively). In addition, nulliparity was also associated with gastroschisis. Independent of maternal age, paternal age, and maternal ethnicity, the birth prevalence increased 3.2-fold (95% CI, 2.3-4.3) during the 17-year study period.

Conclusions The birth prevalence of gastroschisis continues to increase in California, and young, nulliparous women are at the greatest risk of having a child with gastroschisis. *(J Pediatr 2008;152:807-11)*

Gastroschisis, a congenital abdominal wall defect, has a fetal and neonatal mortality rate <10%.[1-4] Although the mortality rate is low, associated morbidities such as bowel atresias and susceptibility to sepsis can lead to prolonged hospitalizations.[4] As a result of the increased survival and subsequent in-hospital complications, the cost of treatment of gastroschisis is high.[5] The average length of hospital stays for newborns was longest in the infants with gastroschisis (41.0 days).[6] In addition, the most expensive average neonatal hospital charges for non-cardiac birth defects were for gastroschisis and congenital diaphragmatic hernia (>$150,000).[6]

The pathophysiology of this defect is not completely understood, but may be a result of an ischemic event from the developmental disruption of the right omphalomesenteric artery.[7] Several population-based studies have explored factors associated with gastroschisis risks. The birth prevalence is strongly associated with young maternal age; compared with women >30 years of age, women <20 years of age have 16-times greater risk of having pregnancies complicated with gastroschisis.[8] Other maternal factors, such as low socioeconomic status, primigravida, poor nutritional status as determined with low body-mass-index, tobacco smoking, and prenatal use of illicit drugs, aspirin, and vascoconstrictive medications, such as pseudoephedrine, have also been implicated.[8-21]

The birth prevalence of gastroschisis has been reported to increase 2- to 4-fold worldwide for the past 3 decades.[22-28] The underlying reasons for this increase are unknown, but they include indications of putative factors resulting in true increased birth prevalence and variable ascertainment with time resulting in spurious increases.

By using data from a population-based registry in California, our objective was to examine potential time trends in prevalence and investigate potential risk factors of gastroschisis in a population of >3.5 million California births.

METHODS

Data were derived from the California Birth Defects Monitoring Program (CBDMP), a population-based active surveillance system for collecting information on births with congenital malformations in California. The data collection procedure consisted of 3 steps: case finding (review of all logs from hospitals and genetic medical centers to find potential cases), culling (chart review to identify the reportable cases from potential cases

CBDMP California Birth Defects Monitoring Program

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Table I. Distribution of study population

Epidemiologic factors	Total births (n = 3524870)	Cases (n = 908)	Birth prevalence (per 10,000 births)
Maternal age (years)			
12-15	34622	33	9.53
16-19	399439	309	7.74
20-24	901856	360	3.99
25-29	1000784	139	1.39
30-34	768739	46	0.60
35-39	345410	15	0.43
40-55	74020	6	0.81
Paternal age (years)	N = 3268187	N = 835	
12-15	4222	2	4.74
16-19	155445	146	9.39
20-24	640421	349	5.45
25-29	897327	191	2.13
30-34	820371	87	1.06
35-39	475686	37	0.78
40-90	274715	23	0.84
Maternal education	N = 2916628	N = 778	
Less than high school	1086053	360	3.31
High school only	857039	265	3.09
College	973536	153	1.57
Paternal education	N = 2718107	N = 656	
Less than high school	930552	257	2.76
High school only	839384	278	3.31
College	948171	121	1.28
Maternal ethnicity	N = 3510415	N = 901	
Non-Hispanic white	1236644	320	2.59
US-born Hispanic	526483	231	4.39
Foreign-born Hispanic	1091382	230	2.11
Black	253857	52	2.05
Asian	246985	41	1.66
Others	155064	27	1.74
Parity	N = 3521549	N = 906	
No earlier birth	1377017	587	4.26
1 earlier births	1077765	206	1.91
2 earlier births	590685	66	1.12
≥3 earlier births	476082	47	0.99
Plurality	N = 3526421	N = 908	
Singleton	3444963	891	2.59
Twins or more	81458	17	2.09
Infant sex	N = 3526378	N = 907	
Male	1803817	459	2.54
Female	1722561	448	2.60

on the basis of the registry's criteria), and abstracting (abstraction of diagnostic and demographic information for each reportable case). Potential cases included all live births, stillbirths (≥20 weeks gestation), and therapeutic abortions.[29] Ascertainment of structural anomalies diagnosed within 1 year of delivery has been estimated as 97% complete.[30] During the 17-year study period (1987-2003), counties monitored by the CBDMP varied because of changes in funding. These county variations in monitoring were unlikely to impact results because computed prevalence ratios were based only on the counties (numerator and denominator) monitored by the CBDMP. Although Torfs et al has published several epidemiologic studies of risk factors for gastroschisis with a California-based sample, these studies overlap only minimally.[16-18] The monitoring program identified infants in whom abdominal wall defects, including gastroschisis, omphalocele, and limb-body wall complex, were diagnosed. The abstracts of medical records were subsequently reviewed by one of the authors, a pediatric surgeon, and only infants with a confirmed diagnosis of isolated gastroschisis were eligible for study. Cases with accompanying anomalies or genetic syndromes and cases of potential ruptured omphalocele were excluded from the study.

Demographic information on mothers and infants was obtained from birth and death certificate files. Birth prevalence, described as number of infants with gastroschisis (cases) per 10,000 births (live births and stillbirths), was estimated for these categories: maternal race/ethnicity (non-Hispanic white, US-born Hispanic, foreign-born Hispanic, Black, Asian, or other), maternal and paternal education (<12 years, high school graduate, or college graduate), maternal and paternal age (12-15, 16-19, 20-24, 25-29, 30-34, 35-39, or >40 years), parity (0, 1, 2, or >3), child sex (female or male), plurality (singleton or multiple), and year of birth.

Analysis was performed using SAS software version 9.1.3. Crude prevalence ratios for each of the predictor variables were generated with contingency tables. A Poisson regression model was fitted to estimate the adjusted prevalence ratios, which included the variables that were statistically significant (P value <.05) in the unadjusted analysis and also those variables that have been found to be significant risk factors in earlier publications. To test for linear trend, we included the birth year as a continuous variable in the logistic regression model. Variables found to be significant risk factors for gastroschisis in the Poisson model were included in the logistic regression model to test for temporal trend.

RESULTS

Between the years of 1987 and 2003, 908 cases of gastroschisis were diagnosed in 3,526,506 live births and stillbirths in California, resulting in a birth prevalence of 2.57 per 10,000 births; of the 908 cases, there were 863 live births, 40 stillbirths, and 5 therapeutic abortions. The distribution of the California cohort and the birth prevalence of gastroschisis are illustrated in Table I.

In unadjusted analyses (Table II), young, nulliparous mothers who were US-born Hispanics and had less than a college education showed the highest birth prevalence of gastroschisis. Fathers with less than a college education also had a higher risk in unadjusted analyses. However, paternal and maternal education no longer contributed to the risk for gastroschisis in adjusted analyses, after accounting for maternal age, maternal ethnicity, paternal age, and parity.

Maternal age, paternal age, maternal ethnicity, and parity were the 4 variables that contributed significantly to the risk of gastroschisis in the adjusted analysis (Table II). Mothers <16 years of age had 4.2-times greater birth prevalence of gastroschisis than mothers between the ages of 25 and 29 years (95% CI, 2.5-7.0). This risk decreased with increasing age until the age of 30 years, when the risk remained constant onward. Low paternal age was also associated with a higher prevalence of gastroschisis; compared with fathers who were 25 to 29 years old, fathers who were 16 to 19 years and 20 to 24 years old had a prevalence ratio of 1.6 and 1.5, respectively (95% CI, 1.1-2.1 and 1.2-1.8, respectively). In addition, foreign-born Hispanic and black mothers had lower birth prevalences than non-Hispanic white mothers (both with prevalence ratios of 0.6 and 95% CI, 0.4-0.7 and 0.4-0.9, respectively); in contrast, Asian and US-born Hispanic mothers had similar risks as non-Hispanic white mothers. Nulliparity remained a consistent risk factor for gastroschisis, independent of maternal age in the adjusted analysis; mothers with at least 1 previous pregnancy had a prevalence ratio of 0.6 (95% CI, 0.5-0.8).

Table II. Risk factors for gastroschisis

	Crude		Adjusted	
Epidemiologic factors	**PR**	**95% CI**	**PR**	**95% CI**
Maternal age (years)				
12-15	6.9	4.7-10.0	4.2	2.5-7.0
16-19	5.6	4.5-6.8	2.9	2.1-4.0
20-24	2.9	2.4-3.5	2.1	1.6-2.7
25-29 (ref)				
30-34	0.4	0.3-0.6	0.4	0.3-0.7
35-39	0.3	0.2-0.5	0.4	0.2-0.7
40-55	0.6	0.3-1.3	0.5	0.2-1.6
Paternal age (years)				
12-15	2.2	0.6-8.9	0.7	0.2-3.9
16-19	4.4	3.6-5.5	1.6	1.1-2.1
20-24	2.6	2.2-3.1	1.5	1.2-1.8
25-29 (ref)				
30-34	0.5	0.4-0.6	0.9	0.6-1.2
35-39	0.4	0.3-0.5	0.9	0.6-1.4
40-90	0.4	0.3-0.6	1.3	0.7-2.2
Maternal education				
Less than high school	1.1	0.9-1.3	1.1	0.9-1.4
High school only (ref)				
College	0.5	0.4-0.6	0.9	0.7-1.1
Paternal education				
Less than high school	0.8	0.7-1.0	0.9	0.7-1.1
High school only (ref)				
College	0.4	0.3-0.5	0.7	0.6-1.0
Maternal ethnicity				
Non-Hispanic white (ref)				
US-born Hispanic	1.7	1.4-2.0	1.0	0.8-1.2
Foreign-born Hispanic	0.8	0.7-1.0	0.6	0.5-0.7
Black	0.8	0.6-1.1	0.6	0.4-0.9
Asian	0.6	0.5-0.9	0.9	0.6-1.3
Others	0.7	0.5-1.0	0.7	0.4-1.1
Parity				
No earlier birth (ref)				
1 earlier births	0.5	0.4-0.5	0.6	0.5-0.8
2 earlier births	0.3	0.2-0.3	0.4	0.3-0.6
≥3 earlier births	0.2	0.2-0.3	0.4	0.3-0.8
Plurality				
Twins or more	0.8	0.5-1.3		
Infant sex				
Female	1.0	0.9-1.2		

Adjusted analysis included maternal age and education, paternal age and education, maternal race, and parity in the model.
PR, Prevalence ratio.

The overall birth prevalence of gastroschisis in California increased significantly from 1987 to 2003 (Figure). In addition, the rate of increase was most notable in mothers <19 years of age. Maternal age and ethnicity and paternal age were included in the regression model to estimate the temporal trend of gastroschisis. Although parity was a significant risk factor for gastroschisis in the adjusted analysis, we excluded parity from the analysis for linear trend because it was

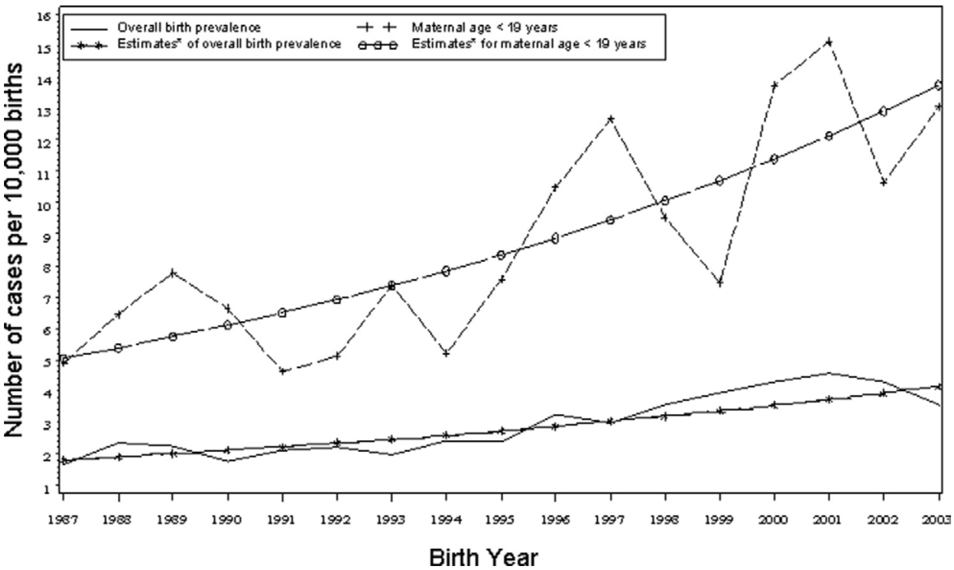

Figure. Birth prevalence of gastroschisis from 1987 to 2003. *Estimates were calculated from the Poisson regression model that controlled for maternal age, maternal ethnicity, and paternal age.

highly correlated with maternal age. For the 17-year study period, the overall birth prevalence increased by 3.2-fold (95% CI, 2.3-4.3; $P < .0001$).

DISCUSSION

This study demonstrated that the birth prevalence of gastroschisis has been gradually rising in the past 2 decades in California, independent of the 3 most significant risk factors, young maternal age, maternal ethnicity, and young paternal age. The strength of this study was the ascertainment system of the CBDMP. The registry was large, population-based, and also applied consistent detection procedures in the 17-year study period. Limitations of this study included potential incomplete ascertainment of elective terminations in California. However, these cases did not contribute significantly to the overall birth prevalence and therefore are unlikely to affect the estimates calculated in this study.

Young maternal age was a strong risk factor for gastroschisis in earlier studies and was reiterated in our results.[18,22,24,26-28,31-33] Several epidemiological studies have supported the theory that young, nulliparious, and socially disadvantaged women were at highest risk of having a child with gastroschisis.[18,22,25] In our study, maternal education served as a potential surrogate marker for socioeconomic status. However, lower maternal education was not a significant risk factor in adjusted analysis, after inclusion of maternal age, which was highly correlated with maternal education. The role of maternal ethnicity in the risk for gastroschisis has not been well-documented secondary to different definitions for subgroups of race and ethnicity in earlier publications.[24,25,34] Our study showed a decreased risk in black and foreign-born women compared with non-Hispanic white women. It is unclear whether the association represents true differences in ethnic groups or whether maternal ethnicity was a proxy for an unmeasured variable, such as socioeconomic or nutritional status. Similar to the report published in Norway, young paternal age played a significant role in the risk of gastroschisis in our cohort.[26] In our study, young paternal age and maternal age were highly correlated. Young paternal age played a smaller role in the risk for gastroschisis than young maternal age. The differences of risk factors for gastroschisis found in the various studies in the literature illustrate the differences among the characteristics of the various study populations. However, the 1 consistent risk factor for gastroschisis remains young maternal age.

The observed secular trend of gastroschisis has been reported in earlier publications. Canada, Norway, the United Kingdom, and Western Australia have published data supporting the unexplained increasing prevalence of gastroschisis since the 1960s.[26,32,33,35] In addition, several states, including Hawaii, North Carolina, Texas, and Utah, have reported similar results.[24,27,36,37] However, these studies varied in their ascertainment procedures. The different state- and country-based birth registries were passive and only included live births, and hospital databases consisted of cases from a single referral tertiary center. The study that used methods most comparable to our investigation was done in Atlanta, Georgia, with the data from the Metropolitan Atlanta Congenital Defects Program from 1968 to 2000. In contrast to previously reported results, Williams et al showed that there was a small increase in the prevalence of gastroschisis after 1975, but the prevalence was relatively unchanged afterward. However, although the registry in Atlanta encompassed a long study period of 33 years, only 211 cases of gastroschisis were found, a small number compared with the 908 cases in our study.[28] Thus, the differences found between the California and Atlanta studies could have been the result of differing population characteristics, although both registries incorporated similar methods of ascertainment.

Our results indicated an increasing birth prevalence of gastroschisis between 1987 and 2003. The explanation for this pattern is unknown. Earlier studies had documented the increased prevalence of gastroschisis only within the group of younger mothers (age <25 years), who are at the highest risk.[22,27,35] However, our results showed that the prevalence increased independent of maternal age and ethnicity, suggesting a potential change in overall population characteristics and not only confined to young mothers. The underlying reasons for the increasing prevalence with time is unknown. The increase could be related to a change in a putative exposure or behavior that has yet to be elucidated. In addition, we speculate that the observed increasing prevalence could be a consequence of either increasing numbers of fetuses with this malformation surviving to detection because of improved maternal nutrition or secular change in environmental exposures. It is important to emphasize that this increasing trend is not isolated to any single demographic or geographic distribution, but has been demonstrated in several, but not all, locations where it has been studied, despite the variable characteristics of these locations.[38]

In conclusion, our study supports the observation of the increasing birth prevalence of gastroschisis, and young maternal age remains the most consistent significant risk factor. The impact of this growing prevalence is magnified in the setting of the unchanged or steady decline of other birth defects, such as omphalocele, another congenital abdominal wall defect.[25,26] Gastroschisis is not a lethal anomaly, and increased hospital costs for patients with this defect represent both improved clinical treatment of these patients in the neonatal period and also the overall increasing birth prevalence. We recommend early diagnosis through prenatal ultrasound scanning and referral to tertiary care center to help minimize postnatal morbidity associated with sepsis and poor nutrition. However, to further understand the pathophysiology of gastroschisis and perhaps to develop preventive measures, future studies are indicated to better examine the potential role of environmental factors in the risk for gastroschisis and gene-environment interactions. In addition, it is important to improve methods of ascertainment across locations to provide better estimates of the true prevalence of gastroschisis and to allow for comparison and contrast in different populations.

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