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Epidemiology of Gastroschisis: A Population-Based Study in California from 1995-2012

Jamie E. Anderson, MD MPH, Laura A. Galganski, MD, Yvonne Cheng, MD PhD MPH, Rebecca A. Stark, MD, Payam Saadai, MD, Jacob T. Stephenson, MD, and Shinjiro Hirose, MD

Division of Pediatric General, Thoracic, and Fetal Surgery, University of California, Davis Medical Center; Sacramento, CA

Abstract

BACKGROUND—Although the incidence of gastroschisis is increasing, risk factors are not clearly identified.

METHODS—Using the Linked Birth Database from the California Office of Statewide Health Planning and Development from 1995–2012, patients with gastroschisis were identified by ICD-9 diagnosis/procedure code or birth certificate designation. Logistic regressions examined demographics, birth factors, and maternal exposures on risk of gastroschisis.

RESULTS—The prevalence of gastroschisis was 2.7 cases per 10,000 live births. Patients with gastroschisis had no difference in fetal exposure to alcohol ($p=0.609$), narcotics ($p=0.072$), hallucinogenics ($p=0.239$), or cocaine ($p=0.777$), but had higher exposure to unspecified/other noxious substances (OR 3.27, $p=0.040$; OR 2.02, $p=0.002$). Gastroschisis was associated with low/very low birthweight (OR 5.08–16.21, $p<0.001$) and pre-term birth (OR 3.26–10.0, $p<0.001$). Multivariable analysis showed lower risk in black (OR 0.44, $p<0.001$), Asian/Pacific Islander (OR 0.76, $p=0.003$), and Hispanic patients (OR 0.72, $p<0.001$) compared to white patients. Risk was higher in rural areas (OR 1.24–1.76, $p=0.001$). Compared to women age <20 , risk decreased with advancing maternal age (OR 0.49–OR 0.03, $p<0.001$). Patients with gastroschisis had increased total charges (\$336,270 vs. \$9,012, $p<0.001$) and length of stay (38.1 vs. 2.9 days, $p<0.001$). Mortality was 4.6%.

CONCLUSIONS—This is the largest population-based study summarizing current epidemiology of gastroschisis in California.

Keywords

Gastroschisis; California; Epidemiology; fetal exposure

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Corresponding Author: Jamie Anderson, UC Davis Medical Center, 2215 Stockton Boulevard, OP512, Sacramento, CA 95817, jeanderson@ucdavis.edu, Phone: 530-300-8611, Fax: 916-453-2035.

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INTRODUCTION

There is evidence the prevalence of gastroschisis is increasing worldwide, [1–7] but the etiology of gastroschisis is not well understood. Young maternal age is the most commonly cited risk factor,[1,5, 8] but it is unclear whether the risk is inherent in young women or is simply a confounder for another exposure that is more common in younger women. Interestingly, the incidence of gastroschisis is increasing for women of all ages, not solely in younger women.[1] Other cited risk factors include white race,[9] nulliparity,[10] tobacco use,[10] sexually transmitted diseases,[11] exposure to non-steroidal anti-inflammatory drugs,[12] exposure to vasoconstrictors,[13] and exposure to herbicides (atrazine),[10, 14] among others.

The aim of this study is to identify trends in epidemiology, risk factors, and outcomes of gastroschisis using a population database in California, one of the most populous and diverse states in the U.S.

1. MATERIALS AND METHODS

This is a retrospective, observational population analysis using data from the Linked Birth Database from the California Office of Statewide Health Planning and Development from 1995–2012. This database includes information on all births in California, including infant birth records and readmissions within one year as well as maternal antepartum and postpartum hospital records. It links information from the following datasets: California Patient Discharge Data, Vital Statistics Birth/Death Certificate Data, Vital Statistics Fetal Death Data, and Vital Statistics Birth Cohort File.

Patients with gastroschisis were identified by an ICD-9 procedure code for gastroschisis repair (54.71); ICD-9 diagnosis code for gastroschisis (756.73, available since 2009); or birth certificate designation for gastroschisis (available since 2006).

Maternal factors included race, ethnicity, age, highest educational level achieved, county of residence, and birth history. Counties were identified as rural, partially rural (metropolitan counties with some rural census tracts), and metropolitan, according to 2010 census data. [15]

Birth data included method of delivery, whether or not the patient labored (regardless of whether Caesarean section was ultimately performed), and time of day of delivery. Season of conception and birth were also identified.

Fetal exposure to certain substances were identified by ICD-9 diagnosis codes. Drug exposures included: alcohol (760.71), narcotics (760.72), hallucinogenics (760.73), cocaine (760.75), unspecified noxious substances (760.70), and other noxious substances (760.79).

Length of stay, total charges during birth hospitalization, and mortality were compared between patients with and without gastroschisis using Student's t-test, non-parametric equality of medians test, and Chi-squared analyses. Univariate and multivariable logistic

regressions examined demographics, birth factors, and maternal exposures on the risk of gastroschisis.

Statistical analysis was performed using Stata/SE version 14.2. This study was approved by the UC Davis Institutional Review Board and the California Committee for the Protection of Human Subjects.

2. RESULTS

From 1995–2012, 2,527 infants with gastroschisis were born in California, resulting in a population prevalence of 2.7 cases per 10,000 live births during the study timeframe (Table 1). The prevalence increased during this time period from 1.5 to 5.3 cases per 10,000 live births.

2.1 Demographics

On unadjusted analysis of race, the prevalence was highest in the white population (2.81 cases per 10,000 live births) and other racial groups (3.31 cases per 10,000 live births), and lowest in the Asian/Pacific Islander population (1.46 cases per 10,000 live births; Table 1). Patients of Hispanic ethnicity also had higher than overall prevalence rates at 3.03 cases per 10,000 live births.

Prevalence differences by race were consistent on univariate logistic regression (Table 2). Compared to white non-Hispanic patients, black/African American or Asian/Pacific Islander patients had decreased odds of gastroschisis (OR 0.69, $p<0.001$; OR 0.52, $p<0.001$), whereas Native American/Eskimo and other racial groups had higher odds (OR 1.61, $p=0.040$; OR 1.17, $p=0.002$). On univariate analysis, odds ratios were also increased among Hispanic ethnicity (OR 1.25, $p<0.001$).

Compared to patients with government insurance for prenatal care, patients with private insurance or self-pay had decreased odds ratios of gastroschisis (OR 0.51, $p<0.001$; OR 0.43, $p<0.001$, respectively).

Compared to women age<20, odds of gastroschisis decreased with advancing maternal age (age 20–24: OR 0.52, $p<0.001$; age 25–29: OR 0.18, $p<0.001$; age 30–34: OR 0.08, $p<0.001$; age 35+: OR 0.03, $p<0.001$).

2.2 Prenatal and Birth Characteristics

There was no difference in length of time of prenatal care between patients with and without gastroschisis (Table 3). While there was no difference in season of conception, patients with gastroschisis were more likely to be born in the fall compared to the spring (OR 1.13, $p=0.030$). Patients with gastroschisis were not more likely to be born at night (between 5:00 PM and 7:00 AM), and were less likely to be born on the weekend (OR 0.84, $p=0.001$).

Mothers of patients with gastroschisis were less likely to be allowed to labor (OR 0.32, $p<0.001$) and much more likely to give birth via Caesarean section (OR 3.29, $p<0.001$). The proportion of patients with gastroschisis undergoing Caesarean section has not changed over

time ($p=0.079$, data not shown). Patients with gastroschisis were more likely to be born pre-term and with low birth weight (<2.5 kg). Multiple births were less likely with gastroschisis (OR 0.58, $p<0.001$).

2.3 Fetal exposures

Patients with gastroschisis had increased odds of exposure to unknown drugs or other noxious substances, but not specifically to alcohol, cocaine, narcotics, or hallucinogenics (Table 4).

2.4 Multivariable logistic regression

In a model including the most significant risk factors for gastroschisis, multivariable logistic regression showed lower odds of gastroschisis among black (OR 0.44, $p<0.001$), Asian/Pacific Islander (OR 0.76, $p=0.003$), and Hispanic patients (OR 0.72, $p<0.001$) compared to white, non-Hispanic patients (Table 5). Importantly, the increase in odds of gastroschisis with Hispanic ethnicity seen on univariate analysis is decreased when including these additional variables. Consistent with the univariate analyses, the multivariable regression demonstrated a decrease in risk with an increase in maternal age (compared to women <20 , OR 0.49–0.03, $p<0.001$); and an increase in risk in partially rural (OR 1.24, $p=0.001$) and rural counties (OR 1.76, $p<0.001$) compared to urban counties. Multivariable regression confirmed an increase in risk over time and an increased risk with unknown or other noxious drug exposures (OR 1.58, $p=0.005$).

2.5 Outcomes

Overall, 104 patients with gastroschisis (4.6%) died (Table 6). Median age of death was 26.5 days (IQR 4.5–83 days). There was no difference in the mortality rate among patients with gastroschisis over time ($p=0.060$). The mortality rate among patients with gastroschisis was higher in patients who were born pre-term (<37 weeks) versus term (5.6% vs. 3.6%, $p=0.027$), but there was no difference comparing low-birth weight (<2.5 kg) to normal birth weight ($p=0.225$). Mean length of stay among patients with gastroschisis was significantly higher than patients without gastroschisis (38.1 days vs. 2.9 days, $p<0.001$). Total charges averaged over \$336,000 for patients with gastroschisis, which was significantly higher than the \$9,102 in patients without gastroschisis ($p<0.001$).

3. DISCUSSION

The prevalence of gastroschisis in California from 1995–2012 was 2.7 cases per 10,000 live births, but has increased during this time period from 1.5 to 5.3 cases per 10,000 live births. The increasing prevalence in California is concordant with ongoing concerns of a worldwide increase in the prevalence of gastroschisis.[1–7]

The highest risk in California continues to be among mothers who are white, young, and live in rural areas. Although mothers of Hispanic ethnicity had higher unadjusted prevalence rates of gastroschisis, risk of gastroschisis in mothers of Hispanic ethnicity was actually lower than non-Hispanic mothers in a multivariable analysis adjusting for other factors. These findings are similar to other states; in a study of 14 states in the U.S. (including

California), unadjusted prevalence was highest among non-Hispanic white mothers, followed by Hispanic mothers, then non-Hispanic black mothers in women less than age 25. [3]

Several other studies have found that the risk of gastroschisis is higher in rural areas,[8] but this has not been extensively studied in California. The higher risk in rural areas has previously been attributed to agricultural exposures, such as atrazine.[10,14] Although we were unable to analyze environmental or agricultural exposures in detail in this study, the risk of gastroschisis did not vary by season of conception, decreasing the likelihood that this geographic difference is due to agricultural exposures that are typically seasonal.

Among fetal drug exposures, risk is only highest among unknown or other drugs or noxious substances, not alcohol, cocaine, narcotics, or hallucinogenics. It is impossible to determine what these other drugs or noxious substances may be, but marijuana and methamphetamine would likely be included in these categories. Given the association of gastroschisis with vasoconstricting medications,[13] maternal exposure to methamphetamines may be a risk factor for gastroschisis. Future studies are certainly needed to determine the relationship of marijuana and methamphetamines to gastroschisis.

Given these findings, younger, white mothers in rural areas of California may have other exposures beyond agricultural contaminants that increase risk of gastroschisis in this population. These young mothers remain vulnerable and efforts should continue to seek to identify risk factors and monitor further increases in prevalence of gastroschisis in this population.

Consistent with the literature, patients with gastroschisis are still more likely to be born pre-term and with low birth weight. Mothers are also still less likely to be allowed to labor and more likely to give birth via Caesarean section. We also found that Caesarean section rates in gastroschisis have not changed over time in California. Other studies suggest that mode of delivery is not associated with survival of infants with gastroschisis;[16] we thus would expect to see these practices change to increase rates of spontaneous labor and decrease rates of Caesarean section.

We calculated a one-year mortality rate of 4.6%, which is higher than in other studies. In a cohort of 393 patients with gastroschisis in the U.K. and Ireland from 2006–2008, the mortality rate was 1.5%, [17] and in a cohort of 409 patients with gastroschisis in Canada from 2005–2010, the mortality rate was 3.2%. [18] Although these studies are not exactly analogous as their follow-up period was limited to the birth admission, the higher mortality rate and the lack of improvement over time in this study are concerning. Since neonates with gastroschisis who were born pre-term had higher mortality rates than those born at term, interventions to prolong pregnancy until term is one potential solution in this population.

We also identified a mean length of stay of 38.1 days and total charges averaging over \$336,000. Although patients with gastroschisis typically have relatively good long-term outcomes, especially compared to other congenital anomalies or pediatric surgical emergencies, it is important to remember that even in California, this congenital anomaly does have significant mortality, morbidity, and cost. Being cognizant of this mortality rate

and other outcomes is useful for counseling and preparing parents of patient with gastroschisis.

3.1 Limitations

The primary limitation is that this study uses hospital discharge data and thus relies accurate physician chart documentation and accurate coding to correctly identify cases of gastroschisis. Birth certificate designations for congenital anomalies (including gastroschisis and omphalocele, separately) were created in 2006. Thus, the accuracy in identifying cases of gastroschisis has increased since 2006. Prior to 2009, the ICD-9 diagnosis code for gastroschisis also included omphalocele, so was not used in this analysis. It is thus possible we missed some cases of gastroschisis prior to 2006 since we were unable to distinguish these cases from omphalocele.

We are also unable to distinguish between the severity/type of gastroschisis (i.e. simple versus complex) or clarify type of closure performed. Epidemiology and outcomes may vary by these groups.

Identifying accurate fetal drug exposures is somewhat limited using ICD-9 diagnosis coding. For example, the drugs or substances included with unknown or other noxious substances are unclear (ICD-9 diagnosis codes 760.70, 760.79). Many of these challenges are improved with ICD-10 coding, but we are unable to tease out specific exposures with the current data.

There may also be a Hawthorne effect related to fetal exposures; mothers of patients with gastroschisis may be more heavily questioned on their drug use and other exposures. This may have artificially increased the risk of other or unspecified noxious or drug exposures.

3.2 Conclusion

The risk of gastroschisis continues to be highest in young, white mothers, and in rural counties. The prevalence is also increasing in California. Although the mortality is relatively low (4.7%), the prolonged hospitalization (>30 days) and high hospital charges (>\$300,000) signify the ongoing high morbidity and cost of this congenital anomaly.

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Table 1.

Patient demographics and unadjusted prevalence by race

	All patients (n=9,306,007)	Gastroschisis (n=2,527, 0.03%)	Without Gastroschisis (n=9,303,480, 99.97%)	P-Value	Cases per 10,000 live births
Female sex – n (%)	4,543,692 (48.8)	1,213 (48.0)	4,542,479 (48.8)	0.701	2.67
Race – n (%)				<0.001	
White	5,941,180 (64.9)	1,667 (67.3)	5,939,513 (64.9)		2.81
Black	551,366 (6.0)	106 (4.2)	551,260 (6.0)		1.92
Asian/Pacific Islander	947,926 (10.4)	138 (5.6)	947,788 (10.4)		1.46
Other	1,710,065 (18.7)	566 (22.8)	1,709,499 (18.7)		3.31
Hispanic ethnicity – n (%)	4,221,896 (46.6)	1,282 (52.2)	4,220,614 (46.6)	<0.001	3.03

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Table 2.

Univariate logistic regressions predicting gastroschisis: Demographics

Variable	Odds Ratio (95% CI)	P-Value
<i>Patient demographics</i>		
Female sex	0.97 (0.89–1.05)	0.403
Race:		
White	Ref	
Black	0.69 (0.56–0.83)	<0.001
Asian/Pacific Islander	0.52 (0.44–0.62)	<0.001
Native American/Eskimo	1.61 (1.02–2.52)	0.040
Other	1.17 (1.06–1.29)	0.002
Hispanic ethnicity	1.25 (1.16–1.35)	<0.001
Insurance (Prenatal):		
Government (MediCare, MediCal, etc.)	Ref	
Private	0.51 (0.47–0.56)	<0.001
Self-pay/no charge	0.43 (0.32–0.59)	<0.001
<i>Maternal demographics</i>		
Age <20	Ref	
20–24	0.52 (0.47–0.56)	<0.001
25–29	0.18 (0.16–0.20)	<0.001
30–34	0.08 (0.08–0.10)	<0.001
35+	0.03 (0.02–0.04)	<0.001
Urban vs. rural county		
Urban	Ref	
Metropolitan counties with some rural census tracts	1.60 (1.42–1.81)	<0.001
Completely rural	3.04 (2.37–3.89)	<0.001

Table 3.

Univariate logistic regressions predicting gastroschisis: Prenatal and birth characteristics

Variable	Odds Ratio (95% CI)	P-Value
Months of prenatal care		
0	Ref	
1–3	1.15 (0.66–1.98)	0.624
4–6	1.34 (0.77–2.32)	0.298
7–9	1.07 (0.60–1.92)	0.810
Season of conception		
Spring	Ref	
Summer	0.96 (0.85–1.07)	0.455
Fall	1.10 (0.98–1.23)	0.106
Winter	0.92 (0.83–1.03)	0.155
Season of birth		
Spring	Ref	
Summer	1.05 (0.94–1.17)	0.440
Fall	1.13 (1.01–1.27)	0.030
Winter	0.94 (0.84–1.05)	0.279
Night birth (between 5 PM and 7 AM)	0.95 (0.88–1.03)	0.193
Weekend birth	0.84 (0.77–0.93)	0.001
Emergent (not scheduled) admission	1.14 (1.04–1.25)	0.003
Allowed to labor	0.32 (0.30–0.35)	<0.001
Caesarean section	3.29 (3.05–3.56)	<0.001
Gestational age at birth		
Term (37+ weeks)	Ref	
Moderate/late pre-term (32–36.6 weeks)	10.0 (9.23–10.89)	<0.001
Very preterm (28–31.6 weeks)	4.98 (3.87–6.41)	<0.001
Extremely preterm (<28 weeks)	3.26 (2.24–4.75)	<0.001
Birth weight		
>4.2 kg	0.16 (0.08–0.29)	<0.001
2.5–4.2 kg	Ref	
1.5–2.49 kg	16.21 (14.97–17.55)	<0.001
<1.5 kg	5.08 (4.04–6.37)	<0.001
Multiple births	0.58 (0.43–0.78)	<0.001

Table 4.

Univariate logistic regressions predicting gastroschisis: Fetal exposures

Variable	Odds Ratio (95% CI)	P-Value
Drug exposure (any of the following)	1.87 (1.34–2.61)	<0.001
Alcohol	1.67 (0.23–11.85)	0.609
Cocaine	1.15 (0.43–3.07)	0.777
Narcotics	1.82 (0.95–3.51)	0.072
Hallucinogenic	2.30 (0.57–9.19)	0.239
Noxious substance (other drugs)	3.27 (1.05–10.15)	0.040
Other noxious substances	2.02 (1.29–3.18)	0.002

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Table 5.

Multivariable logistic regression predicting gastroschisis

Variable	Odds Ratio (95% CI)	P-Value
Race:		
White	Ref	
Black	0.44 (0.36–0.55)	<0.001
Asian/Pacific Islander	0.76 (0.64–0.91)	0.003
Native	1.19 (0.73–1.92)	0.482
American/Eskimo	1.05 (0.94–1.16)	0.394
Other		
Hispanic	0.72 (0.65–0.78)	<0.001
Maternal age (years):		
<20	Ref	
20–24	0.49 (0.44–0.53)	<0.001
25–29	0.16 (0.14–0.18)	<0.001
30–34	0.07 (0.06–0.09)	<0.001
35+	0.03 (0.02–0.04)	<0.001
Urban vs. rural county		
Urban	Ref	
Metropolitan counties with some rural census tracts	1.24 (1.10–1.40)	0.001
Completely rural	1.76 (1.36–2.28)	<0.001
Year of birth		
1995	Ref	
1996	0.96 (0.71–1.30)	0.787
1997	0.92 (0.68–1.25)	0.608
1998	0.90 (0.66–1.23)	0.519
1999	1.06 (0.79–1.43)	0.682
2000	0.94 (0.69–1.28)	0.692
2001	1.37 (1.03–1.81)	0.028
2002	1.15 (0.86–1.54)	0.356
2003	1.50 (1.13–1.97)	0.004
2004	1.31 (0.99–1.75)	0.062
2005	1.19 (0.89–1.59)	0.239
2006	2.18 (1.69–2.82)	<0.001
2007	2.33 (1.81–3.00)	<0.001
2008	2.26 (1.75–2.92)	<0.001
2009	2.63 (2.04–3.38)	<0.001
2010	2.93 (2.28–3.76)	<0.001
2011	3.40 (2.66–4.35)	<0.001
2012	3.79 (2.97–4.84)	<0.001
Drug exposure *	1.58 (1.01–2.49)	0.005

* Includes other and unknown noxious substances.

Table 6.

Outcomes during birth hospitalization

	All patients (n=9,306,007)	Gastroschisis (n=2,527, 0.03%)	Without Gastroschisis (n=9,303,480, 99.97%)	P-Value
Died – n (%)	43,034 (0.5)	104 (4.6)	42,930 (0.5)	<0.001
Length of stay – mean (days), 95% CI	2.8 (2.9–2.9)	38.1 (36.5–39.6)	2.9 (2.9–2.9)	<0.001
Total charges – mean (\$), 95% CI	9,101 (9,060–9,142)	336,270 (317,703–354,837)	9,012 (8,971–9,053)	<0.001

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