Respiratory outcomes in the first ten years-of-life in children with gastroschisis: a retrospective cohort study

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ABSTRACT

Background

Little attention has been given to the long-term respiratory outcomes of children with gastroschisis. The purpose of this study was to determine if gastroschisis survivors have more respiratory illnesses in their first 10 years-of-life compared to age-matched controls.

Methods

We performed a retrospective cohort study of all gastroschisis children born in Manitoba between 1991-2017. Gastroschisis cases were identified from a clinical database, and a date-of-birth matched control cohort was constructed from a population-based data repository. International Classification of Disease codes were used to compare the risk and frequency of respiratory diagnoses for children with gastroschisis to date-of-birth matched controls from 0-5 years-of-age and 5-10 years-of-age.

Results

The 0-5 years-of-age analysis included 117 gastroschisis cases and 1205 date-of-birth matched controls; children with gastroschisis had a higher risk of asthma (RR=1.46, 95%CI:1.03,2.55, p=0.029), acute bronchitis/bronchiolitis (RR=1.61, 95%CI:1.27,2.03, p<0.001), pneumonia (RR=1.99, 95%CI:1.45,2.72, p<0.001), viral pneumonia (RR=5.15, 95%CI:1.79,14.81, p=0.007), and pneumonia due to unspecified organism (RR=2.06, 95%CI:1.45,2.92, p<0.001). Gastroschisis children 0-5 years-of-age were also diagnosed more frequently with bronchitis/bronchiolitis (RR=2.14, 95%CI:1.79,2.57, p<0.001) and viral pneumonia (RR=8.10, 95%CI:3.79,17.31, p<0.001). The 5-10 years-of-age analysis included 73 cases and 738 controls;

no difference in the risk of respiratory illness was found for gastroschisis cases and controls in this age group. However, gastroschisis cases were more frequently diagnosed with bacterial pneumonia (RR=3.03, 95%CI:1.67,5.51, p<0.001) and influenza (RR=3.03, 95%CI:1.67,5.51, p<0.001).

Conclusion

Our study shows that children with gastroschisis have an increased risk of asthma and respiratory infections compared to children without gastroschisis, most noticeably in the first 5 years-of-life.

Keywords: gastroschisis, respiratory, outcomes

Level of evidence: 3

Disclosure statement

None of the authors have conflicts of interest to declare.

1. INTRODUCTION

Gastroschisis is a congenital herniation of abdominal viscera through an abdominal wall defect. Recently, the prevalence of gastroschisis has increased [1]. Because improved surgical and peri-operative management has led to a 92% 5-year survival rate [2,3], studies of long-term outcomes are important. Much of the outcome research for gastroschisis survivors has focused on gastrointestinal and anthropometric outcomes; however, respiratory, neurodevelopmental, neurologic, genitourinary, and quality-of-life outcomes of gastroschisis survivors have been increasingly reported.

Respiratory diseases are a major cause of morbidity and mortality in infants and young children[4]. Pneumonia accounted for more than 800,000 pediatric deaths in 2017 and is the leading cause of death in children less than 5 years-of-age [5]. Respiratory distress and recurrent wheezing have been associated with frequent hospital admissions for children [6]. Asthma is the most common non-communicable disease diagnosed, with over 339 million people afflicted world-wide [7]. However, little attention has been given to pulmonary dysfunction in children with a history of gastroschisis, despite evidence that the gastrointestinal and immune systems are interconnected [8].

The primary purpose of this retrospective cohort study was to determine if gastroschisis survivors have more respiratory illnesses in their first 10 years-of-life compared to age-matched controls. The secondary aims were to determine if the frequency with which gastroschisis survivors were diagnosed with respiratory illnesses differed from controls and how the frequency changed with time.

2. METHODS

Ethics approval was granted [HS20964 (H2017:252)]. Winnipeg's Surgical Database of Outcomes and Management (WiSDOM) was used to identify all children diagnosed with gastroschisis in Manitoba between 1991 and 2017. The WISDOM database contains demographic information, treatment details, and short-term outcomes for gastroschisis patients. The WISDOM data was linked to the *Manitoba Centre for Health Policy* through the government department of *Manitoba Health, Seniors and Active Living* using scrambled *Personal Health Identification Numbers*. The *Manitoba Centre for Health Policy* is a repository of population-level data that includes health, education, and socioeconomic details for all people living in Manitoba.

The control cohort was obtained from the *Manitoba Center for Health Policy* using the *Manitoba Health Insurance Registry;* 10 date-of-birth matched controls were randomly selected from the general population for each gastroschisis patient. Scrambled *Personal Health Information Numbers* were used to access the control cohort's data from the *Manitoba Center for Health Policy*. The cohort was created using SAS® statistical software.

Baseline characteristics of cases and controls were collected from the *Hospital Abstracts* data set available from the *Manitoba Center for Health Policy*. The baseline characteristics were: gestational age at birth, birth weight, sex, 1- and 5-minute APGAR scores, length of hospital stay after birth, and socioeconomic status. The maternal *Socioeconomic Factor Index* at time of the child's birth was used as a measure of socioeconomic status. The *Socioeconomic Factor Index* is derived from four variables based on one's residential postal code: 1. the unemployment rate for

individuals more than 15 years-of-age; 2. the average household income for individuals more than 15 years-of-age; 3. the proportion of single parent households; and 4. the proportion of population more than 15 years-of-age without a high school diploma [9]. Postal codes were abstracted from the *Registered Postal Code* dataset from the *Manitoba Center for Health Policy*, and the *Socioeconomic Factor Index-2* methodology was used to calculate the corresponding *Socioeconomic Factor Index* [9].

Cases and controls were divided into two age groups: early childhood (0-5 years-of-age) and late childhood (5-10 years-of-age). We divided the cases and controls into two age groups to explore the temporal relationship between gastroschisis and respiratory outcomes. Analyses included individuals with health care coverage for the entire duration of each age group; this ensured that comparisons included participants with equal probability of outcomes occurring. Therefore, children without health care coverage for the 5 years of the early age group, or the 5 years for the late age group, were excluded from the analyses.

Provincial health care coverage allows residents of Manitoba to access free health care but is terminated in the event of emigration or death. Patients' health care expenses are charged to the provincial health care program through the *Medical Claims/Medical Services* from the *Manitoba Center for Health Policy.* Therefore, health services utilized by every Manitoba resident are recorded.

Respiratory outcomes were identified through the *Medical Claims/Medical Services* data set and *Hospital Abstracts* dataset available from the *Manitoba Center for Health Policy*; the

International Classification of Diseases version 9 (ICD-9) was used to search these data sets. The *Hospital Abstracts* data set contains demographic and clinical information recorded upon discharge from hospital. The *Medical Claims/Medical Services* captures services provided in hospital but also medical services provided in clinics and doctors' offices. Prescriptions for medications to manage respiratory illnesses were available from the *Drug Program Information Network* data set within the *Manitoba Center for Health Policy* using the Anatomical Therapeutic Chemical classification code. The *Drug Program Information Network* is a point-of-sale prescription drug database.

2.1 Risk of respiratory illness

The relative risks of respiratory diagnoses in gastroschisis children were compared to controls. The respiratory diagnoses, and ICD-9 codes, examined were: acute nasopharyngitis (460), acute sinusitis (461), acute pharyngitis (462), acute tonsillitis (463), acute laryngitis and tracheitis (464), acute upper respiratory infection (465), acute bronchitis and bronchiolitis (466), chronic sinusitis (473), viral pneumonia (480), pneumococcal pneumonia (481), other bacterial pneumonia (482), pneumonia due to other organisms (483), pneumonia in infectious diseases classified elsewhere (484), bronchopneumonia organism unspecified (485), pneumonia organisms unspecified (486), influenza (487-488), and asthma (493). Asthma was also examined using the *Drug Program Information Network* to identify prescriptions for inhaled bronchodilators and inhaled steroids. Bronchodilators were defined as medications in the 'inhaled adrenergic' (R03A) or 'inhaled anticholinergic' (R03BB) categories, and steroids as medications in the 'inhaled glucocorticoids' (R03BA) category. Asthma was further examined in the 0-5 age group by determining the incidence of patient and control atopy and the maternal

history of asthma or smoking. Atopy was identified using the 'atopic dermatitis and related conditions' (ICD-9: 691) and 'contact dermatitis and other eczema' (ICD-9: 692) codes to search the *Medical Claims/Medical Services* data set. Maternal asthma and smoking during pregnancy were determined using anonymized maternal *Personal Health Information Numbers* and the *Medical Claims/Medical Services* and *Families First Screen* data sets [10]

2.2 Frequency of respiratory illness

In addition to comparing the risk of being diagnosed with a respiratory illness, we also compared the relative rates, or frequency, of cases and controls being diagnosed with a respiratory illness. This demonstrated not only if children were ever diagnosed, but how many times they received any one diagnosis. The respiratory diagnoses examined were: acute nasopharyngitis, acute upper respiratory tract infection, acute bronchitis and bronchiolitis, chronic sinusitis, viral pneumonia, pneumococcal pneumonia, other bacterial pneumonia, all bacterial (pneumococcal and other bacterial pneumonia), pneumonia due to other organisms, bronchopneumonia, and influenza. We modelled the rates of respiratory diagnoses using a proportional intensity model for recurrent events, an extension of the Cox proportional hazards regression model that can be fit using the coxph function in the survival package in R® [11,12]. The proportional intensity model assumes that the rate of diagnosis remains constant as the baseline rate varies over time. This assumption was explored by looking at the plot of Schoenfeld residuals versus age. We then tested the Pearson's correlation between the residuals and age using the cox.zph function of the survival package in R® [13].

2.3 Statistical analysis

Two-tailed t-tests, Chi-squared tests, and Fisher's exact tests were used to compare continuous and categorical baseline characteristics. Results are reported as means with standard deviations. We reported the risk ratio (RR) and odds ratio (OR) associated with each respiratory diagnosis. The statistical analysis was performed using R® version 3.6.1. P values <0.05 were considered significant.

We used propensity score methods to examine the effect of gastroschisis on respiratory outcomes while controlling for the possible confounding effects of socioeconomic status and sex. The propensity score model for gastroschisis was regressed on socioeconomic status and sex to produce a single linear predictor for how the confounders influenced the occurrence of gastroschisis. The propensity analysis was only applied to diagnoses that had a sufficient sample size (N10).

3. RESULTS

A total of 141 gastroschisis cases were identified in the WiSDOM database. Date-of-birth matching identified 1410 controls from the general population. At the time of the study, 117 cases and 1205 controls had reached their 5th birthday and had received health care for 5 years; these children were included in the 0-5 years analysis. The 14 gastroschisis patients excluded from the 0-5 years analysis had died (n=6) or emigrated out of Manitoba (n=8) at the time of the study. The same criteria excluded 105 controls from the 0-5 years analysis (n=8 died and n=97 emigrated). Similarly, at the time of the study, 73 cases and 738 controls had completed their 10th year-of-life and received health care coverage for 10 years; excluded were 11 cases (n=4 died and n=7 emigrated) and 102 controls (n=7 died and n=95 emigrated).

3.1 Baseline demographics

Compared to controls, neonates with gastroschisis had lower birth weights (2721.30 grams vs. 2466.93 grams, $p<0.001$), lower gestational age (36.50 vs. 39.11, $p<0.001$), lower 1-minute Apgar scores (6.31 vs. 7.91, $p<0.001$), and longer hospital stays at birth (46.30 days vs. 3.01 days, $p<0.001$). Families of children with gastroschisis also had lower socioeconomic status than families of controls ($p<0.001$). Table 1 summarizes these results.

3.2 Children 0-5 years-of-age

3.2.1 Risk of respiratory illness 0-5 years-of-age

Children with gastroschisis 0-5 years-of-age had more respiratory illnesses than children without gastroschisis. Gastroschisis patients had a higher risk of acute bronchitis/bronchiolitis ($p<0.001$) and pneumonia ($p<0.001$). Viral pneumonia ($p=0.007$) and pneumonia due to unspecified organism ($p<0.001$), but not other classifications of pneumonia, were significantly more common in gastroschisis (Table 2). The diagnosis of asthma was more common in gastroschisis children than controls ($p=0.029$); this was supported by our finding that more asthma-associated prescription drugs were dispensed to gastroschisis patients than controls: inhaled bronchodilators ($p=0.01$) and inhaled steroids ($p=0.026$) (Table 3). Although gastroschisis cases did not have increased risks of dermatitis and eczema (RR=1.47, 95%CI:0.18,11.86, $p=0.520$) or maternal asthma (RR=1.15, 95%CI:0.90,1.48, $p=0.286$), gastroschisis mothers were more likely to have smoked during pregnancy (RR=2.93, 95%CI:2.10,4.07, $p<0.001$). Controlling for gender and socioeconomic status with propensity score matching did not change the results.

3.2.2 Frequency of respiratory illnesses 0-5 years-of-age

Gastroschisis children 0-5 years-of-age, were more frequently diagnosed with acute bronchitis/bronchiolitis ($p<0.001$) and viral pneumonia ($p<0.001$) compared to controls (Table 4). The cox.zph model indicated that the increased rate of acute bronchitis/bronchiolitis ($X^2=12.27$, $p<0.001$) and viral pneumonia ($X^2=6.18$, $p=0.013$) varied over the five-year period (Table 4). This indicates that the relative rates, frequencies, were not persistently higher for gastroschisis cases during this time period. The plot of the Schoenfeld residuals suggested that the rate of bronchitis/bronchiolitis was higher in cases from birth until approximately 4 years-of-age (Figure 1). Similarly, the rates of viral pneumonia were higher in cases than controls until approximately 1.5 years-of-age (Figure 2). Severe acute upper respiratory infection ($p=0.011$), acute bronchitis/bronchiolitis ($p<0.001$), and viral pneumonia ($p<0.001$) resulting in hospitalization occurred more frequently in gastroschisis patients (Table 5). The cox.zph model indicated that the increased rate of acute upper respiratory infection ($X^2=0.01$, $p=0.939$), bronchitis/bronchiolitis ($X^2=1.41$, $p=0.240$), and viral pneumonia ($X^2=0.09$, $p=0.764$) did not vary with age over the five-year period (Table 5).

3.3 Children 5-10 years-of-age

3.3.1 Risk of respiratory illness between 5-10 years-of-age

From 5-10 years-of-age gastroschisis children did not have an increased risk of respiratory diagnoses compared to controls (Table 6).

3.3.2 Frequency of respiratory illness 5-10 years-of-age

Compared to controls, gastroschisis children 5-10 years-of-age had a higher rate of acute bronchitis/bronchiolitis ($p=0.005$), bacterial pneumonia ($p<0.001$), and influenza ($p<0.001$) diagnoses (Table 4). The cox.zph model indicated that the increased rate of acute bronchitis/bronchiolitis ($X^2=2.77$, $p=0.096$), bacterial pneumonia ($X^2=2.03$, $p=0.155$), and influenza ($X^2=0.68$, $p=0.410$) did not vary with age over the five-year period (Table 4). There were no severe respiratory illnesses requiring hospital admissions for cases or controls after 5 years-of-age.

4. DISCUSSION

Our study shows that young children with a history of gastroschisis are more likely than controls to be diagnosed with respiratory illnesses, but this disparity resolves with time. Prior to 5 years-of-age, gastroschisis children were more often diagnosed with bronchitis/bronchiolitis and viral pneumonia, and hospitalized for acute respiratory infections, bronchitis/bronchiolitis, and viral pneumonia. Young gastroschisis survivors were also more likely than controls to be diagnosed with asthma and be prescribed inhaled bronchodilators or corticosteroids. Gastroschisis children 5-10 years-of-age were not more likely than controls to have respiratory infections or need treatment for asthma. Controlling for socioeconomic status and gender did not alter any of the analyses, although the p-value for asthma in the 0-5 years-of-age group reached 0.05.

Our research is consistent with three previously published studies on gastroschisis and respiratory disease. Banister et al. showed that gastroschisis children had 27% more respiratory tract infections and double the rate of lower respiratory tract infections compared to children

without gastroschisis [14]. In a study by Andres et al., 21.6% of gastroschisis children were hospitalized with respiratory infections in their first year-of-life [15]. Fasching et al. reported that 32% of gastroschisis children had an episode of bronchitis in the 8 years they were followed [4].

The gastrointestinal system plays an important role in the human immune system as suggested by the large number of immune cells in the gut-associated lymphoid tissue [8]. In gastroschisis, the abdominal viscera are exposed to amniotic fluid causing inflammatory changes in the intestinal wall [16]. The combination of prenatal inflammatory changes and postnatal manipulation required to reduce the viscera and close the abdominal wall defect may compromise the immune function of the gastrointestinal tract in children with gastroschisis. This may disrupt the systemic immune function predisposing young children to infections and/or inflammatory disorders.

The gastrointestinal immune function may be embryologically related to the respiratory immune system. Vighi et al. suggested that the common endodermic origins of the gastrointestinal and respiratory tissues might link the two systems' immune functioning [8]. In addition, it is known that the gut microbiome and the immune system are interconnected; dysbiosis of the gut microbiota can cause immune disfunction and susceptibility to diseases such as asthma [17 18-21]. Therefore, the developmental disruption of the gastrointestinal system seen in gastroschisis patients may indicate a concurrent reduction in immune response: gastroschisis children may be more susceptible to respiratory infections.

A diagnosis of asthma in children younger than 6 years-of-age is controversial. According to Ducharme et al., asthma often starts prior to age 6, however, the inability to perform lung-

function tests on these children makes a formal diagnosis difficult [22]. The presence of atopy or a family history of asthma may support an asthma diagnosis [22]. Our study found more asthma diagnoses and prescriptions for asthma-related drugs in gastroschisis children 0-5 years-of-age. However, we found no increased risk of atopic dermatitis, contact dermatitis or eczema. And, while we found no difference for maternal asthma, we found maternal smoking during pregnancy was significantly higher for cases compared to controls. The increased number of asthma diagnoses, asthma-related prescription drugs and prenatal smoking suggest gastroschisis children 0-5 years-of-age have a higher risk of asthma; however, this finding should be interpreted with caution.

In our study, the respiratory infection rate and frequency were the same for cases and controls in the older age group. The improved respiratory outcomes of older gastroschisis survivors may be due to acquired immunity. For example, attendance at daycare was associated with more colds in preschool years, but it protected against colds during early school years [23].

The effects of social determinants of health on the incidence of gastroschisis have been studied. Younger maternal age and lower socioeconomic status were found to be associated with increased incidence of gastroschisis [24,25]. Lower socioeconomic status is also a risk factor for respiratory disease [26]. However, after controlling for socioeconomic status and sex in our study, the incidence of viral pneumonia and asthma remained higher in patients with gastroschisis than controls prior to 5 years-of-age.

Our study has several limitations. The preferred method of diagnosing of asthma is spirometry. However, in children less than 5 years-of-age spirometry is unreliable as it requires active participation from the child. Only 21% of primary care doctors use spirometry to diagnosis asthma [27]. By relying on administrative datasets, we may have overestimated the true incidence of asthma, particularly in the early childhood analysis. The retrospective nature of our study meant we relied on ICD codes chosen by medical coders. Although, our control cohort was not matched for sex, the propensity score-matched analysis addressed this limitation. Another limitation of our study is the difference in baseline characteristics of the gastroschisis patients and control group. The gastroschisis cohort had lower birthweight, lower gestational age, 1-minute Apgar score, longer length of hospital stays, and were more likely to be born into a family with fewer socioeconomic resources compared to children without gastroschisis. Propensity score matching controlled for the socioeconomic disparity but not the other variables. Finally, we did not control for environmental factors, such as smoking in the household or urban versus rural residences, that could affect respiratory outcomes.

Despite these limitations, our study used a large comprehensive repository of unbiased population level administrative data, allowing us to collect data over a 10-year period without the issues normally associated with longitudinal cohort studies. In addition, our study compared the respiratory outcomes of children born with gastroschisis to a date-of-birth matched control population using a 1:10 ratio. By providing 10 date-of-birth matched controls for every gastroschisis child, we were able to improve the power of our analysis.

5. CONCLUSION

Our study shows that children with gastroschisis have an increased risk for respiratory infections and asthma compared to children without gastroschisis. Although these differences may resolve with time, vigilance is required in early childhood to identify and manage respiratory illnesses in gastroschisis survivors.

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