The Distribution of Gastroschisis in Manitoba

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A capstone project submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements for the degree of MASTER OF PHYSICIAN ASSISTANT STUDIES

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May 27 2015

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Abstract

Introduction: There is a reported increase in prevalence of gastroschisis worldwide. In addition, there are a significant number of hot spots identified in the current literature. The etiology for this increase is largely unknown at this time. It is postulated that one of these notable hot spots is in Northern Manitoba where the prevalence of gastroschisis is higher when compared to the rest of the province and country.

Methods: We conducted a retrospective cohort study and identified cases of gastroschisis through provincial databases and medical records. They were referenced with postal codes and birth rates according to region.

Results: The results demonstrate a 2 to 3 fold increase in prevalence of gastroschisis in the Northern regions of Manitoba when compared to rates in Southern Manitoba.

Conclusion: We successfully identified hot spots in Manitoba that have an increased prevalence of gastroschisis. A variety of risk factors have been identified as etiologies for gastrocschisis. Future research efforts will include further investigations in the population of Northern Manitoba and analysis of specific maternal and geographic considerations that could explain the increase in prevalence.

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Introduction

Gastroschisis (GS) is a defect of the abdominal wall that presents at birth with the prolapse of the abdominal contents, most frequently the intestine (1). It occurs most often to the right of the umbilicus at the junction of the umbilicus and the skin (2). In utero, the prolapsed abdominal contents are exposed to amniotic fluid, which can be caustic to the bowel, causing inflammation. This results in bowel that can be edematous, thick, shortened and covered in a fibrous exudate that makes manual reduction more challenging and often leads to prolonged ileus (1).

There have been a variety of theories postulated to explain the embryological pathogenesis of GS. GS is postulated to be primarily dependent on environmental factors leading to vascular compromise (1) with some authors suggesting an interplay involving environmental factors and genes (3). There are important vascular changes that take place between the fifth and eighth week of gestation to the right of the umbilicus where the site of the defect exists (3). Specifically, the right umbilical vein or right vitelline artery (2,4) involutes and is replaced by the omphalomesenteric artery (3,5).

GS has been described as a pandemic over the last three decades with the last being in 1995 (6). Since the last pandemic, it was estimated that the baseline birth prevalence was 1 in 50,000 but has increased between 10- and 20- fold since (6).

Moore et al. (2013) report a temporal increase in the incidence of GS in many countries including Canada and this is the focus of epidemiologic studies. Based on aggregated data from 2002 to 2009 from the Canadian Congenital Anomalies Surveillance System

(CCASS), prevalence of GS in Canada is 3.7 per 10,000 total births with a gradual increase in prevalence from 3.1 per 10,000 total births (live and still births) in 2002 to 4.4 per 10,000 total births in 2009 (7). This represents a significant increase of 43.8% (7). Furthermore, prevalence of GS amongst provinces and territories was variable with rates ranging from 1.6 (95% CI 1.1-2.4) per total births in Quebec to 19.6 (95% CI 9.4-36.1) per 10,000 total births in Nunavut (4).

In the United States, Kirby et. al reported an increase in prevalence from 2.32 in 1995 to 4.42 in 2005 per 10,000 live births in 15 states (8). Another study testified to a 10-fold increase in prevalence in GS in Utah over 31 years (0.36 to 3.92 cases per 10,000 live births (still births and abortions not included), $P<0.001$ (2). The state of Texas reported a 5.1% increase in prevalence from 1997 to 2000 (9), while the state of North Carolina reported a 130% increase from 1997 to 2000 noted to be due to younger maternal age (10). Internationally, prevalence rates for 2007 varied from as low as 0.7 per 10,000 births in Campania-Italy to a high of 9.4 per 10,000 births in South America (4). Geographical variation has been observed and described as decreasing with latitude from North-to-South in Britain and Ireland (11) and Europe (12).

Young maternal age of less than 25 years old has been a consistently reported risk factor for GS (2,8,13–16) as well as smoking during pregnancy (2,14,17–20). The use of over the counter medications prenatally such as aspirin has been shown to be a risk factor (19,21), whereas studies looking at acetaminophen and pseudoephedrine show discordance in their conclusions (21,22). Ibuprofen and phenylpropanolamine showed no increased risk (21). Periconceptual alcohol consumption (23) and recreational drug use (cocaine, methamphetamines and ecstasy) are significant risk factors (19). Other risk

factors that have been suggested including primigravida status (2), maternal exposure to surface water atrazine and spring conception (24), first trimester maternal stress (25), the use of any antidepressant during pregnancy (14), maternal history of pre-gestational diabetes mellitus 1 or 2 (14), history of gynaecological disease (19) and pre-conceptual or first trimester genitourinary infections (26). Diets with low protein, low zinc and low BMI showed increase risk of GS (18), where higher intake of fruits and vegetables, a longer duration of folic acid supplementation and an increased BMI all reduced risk (17). GS has not been shown to be linked to any major chromosomal or single-gene syndromes (27).

Possible associations between the incidence of GS and ethnicity have been reviewed. A retrospective American study on abdominal wall defects (AWD), specifically GS and omphalocele, observed that women of indigenous ethnicity of North America and the Pacific (Hawaiian, Guamanian, American Indian, Native Alaskan, Samoan) had the highest rates of AWD as compared to other groups (North American (Whites/Blacks), Hispanic, Southeast Asian (Vietnamese, Filipino) and South/East Asian (Korean, Japanese, Asian Indian, Chinese) with Hawaiian's having the highest point estimate (not significant) (28). Williams et al. reported that infants born with GS to teenage mothers were less likely to be born to Black mothers versus White mothers (RR, 0.4; 95% CI 0.2–0.6) (29). An American study observed that maternal race/ethnicity and nativity were associated with significantly higher rates of GS with non-Hispanic black women having the lowest risk (PR, 0.19; 95% CI, 0.13–0.26), followed by Hispanic women (PR, 0.60; 95% CI, 0.43–0.83). Also, women born outside the United States versus U.S.-born women were less likely to give birth to an infant with GS (PR, 0.59;

95% CI, 0.41–0.86) (15). Brindle et al. reported that GS in Canada was frequently seen in young, aboriginal, smoking mothers with worse outcomes been seen in those having single parent status, cocaine use and maternal hometown geographic isolation (30).

Clusters of GS have been reported in Massachusetts and Texas (31) as well as North Carolina after adjusting for partial risk factors such as age, race, parity and smoking (32). It has been postulated amongst the surgical and neonatal specialists that there is an increase prevalence of GS in the Northern communities of Manitoba, more specifically in the northeast corner of Manitoba. We wanted to investigate the prevalence of GS among live born infants in the various communities of Manitoba over the past 6 years. As the phenomenon of GS hot spots has not been investigated in Canada, let alone a specific province, we hope to determine if there is a GS hot spot in Manitoba and if so; how do prevalence rates of this hot spot compare to provincial and national rates. In order to further characterize the hot spots we can suggest possible mechanisms to explain this phenomenon and make suggestions for further research. By looking at hot spots and the population that is compromised, questions regarding aetiology characterization can begin to be answered. Once cause is identified, appropriate prevention strategies or management strategies can be implemented.

Materials and Methods

Data was obtained from the medical records and archives at the Health Sciences Center in Winnipeg, Statistics Canada (SC) and Manitoba Center for Health Policy (MCHP). SC is a legislated service that aims to provide Canadians with relevant high-quality statistics. By using advisory groups, stakeholders as well as a

Census every five years along with hundreds of active surveys on many different aspects related to Canadians, objective statistical information is collected to better serve Canadians, unions, non-profit organizations, businesses and elected representatives. The MHCP is a Winnipeg based research unit out of the University of Manitoba's College of Medicine and Faculty of Health Sciences that is concerned with the health of Manitobans. Their team consists of University researchers, graduate students and system analysts. They obtain anonymized information pertaining to Manitoban's use of physicians, hospitals, prescriptions, etc. from Manitoba Health and stored in a database, the Repository, which can be made available to those seeking access.

We identified cases of congenital malformations diagnosed within the first month of life. We conducted a retrospective cohort study, where cases of GS were identified using the SCD codes between the years of 2009 and 2014. We subsequently identified birth rates per region in Manitoba and did a spatial comparison of incidence of GS per region in Manitoba based on maternal postal codes and census division.

Results

Through medical records in Manitoba we identified a total of 81 cases of GS between 2009 and 2014. 19 cases of GS were identified in 2009/10, 16 in 2010/11, 16 in 2011/12, 13 in 2012/13 and 17 in 2013/14. The Northern Manitoba, Northern Interlake and Winnipeg regions showed higher incidences of GS as compared to others. Notably, of the cases in 2009/10 3 cases were in Northern Manitoba, 5 in the Interlake and 7 in Winnipeg. In 2010/11, 2 were in the northern Manitoba and 1 in the Interlake and 7 in

Winnipeg. In 2011/12 and 2012/14, each year saw 4 cases in the Northern Manitoba region and none in the Interlake with 6 and 8 cases in Winnipeg. In 2013/14 there were 3 cases in northern Manitoba, none in the Interlake and ten in Winnipeg. Between 2009 and 2014, approximately 19.28% of GS cases were identified in the Northern Manitoba region, 7.23% in the Interlake region and 42.17% in Winnipeg exclusively. Areas outside of Northern Manitoba, Northern Interlake and Winnipeg regions saw a grand total of 19 cases or 23.46% of the total number of reported cases between 2009 and 2014. This data is presented in table 1.

Table 1: Number of Cases of GS identified annually in Manitoba between 2009 and 2014 and further represented according to region and percent total per region

		Region					
Year	Total Number of Gastroschisis Cases in MB	Northern Manitoba	North Interlake	Winnipeg	Brandon	Steinbach	Western Manitoba
2009/10	19	3	5	7	1	1	1
2010/11	16	2	1	7	2	0	0
201/12	16	4	0	6	1	0	2
2012/13	13	4	0	8	0	0	0
2013/14	17	3	0	10	0	0	0
Total	81	16	6	38	4	1	3
% of total cases	100	19.75	7.41	46.91	4.94	1.23	3.7

Region							
Thompson	Eastern Manitoba	South West Manitoba	Rual Manitoba	Portage la Prarie	South East Manitoba	South Central Manitoba	Morden
1	0	0	0	0	0	0	0
0	1	1	1	1	0	0	0
0	0	0	0	0	2	1	0

0	0	0	0	0	0	0	1
0	1	0	0	1	0	0	0
1	2	1	1	2	2	1	1
1.23	2.47	1.23	1.23	2.47	2.47	1.23	1.23

Over this period of time, cases of gastroschisis per 10,000 births were calculated according to region by averaging the number of cases in relation to the birth rates in the region by census division. 5-7 cases of gastroschisis were seen in the Northern Manitoba region and 4-5 cases in the Interlake region per 10,000 live births. A rate of 3-4 cases per 10,000 live births was observed in Winnipeg and Southern Manitoba. The number of cases of gastroschisis per 10,000 births according to region is presented in figure 1.

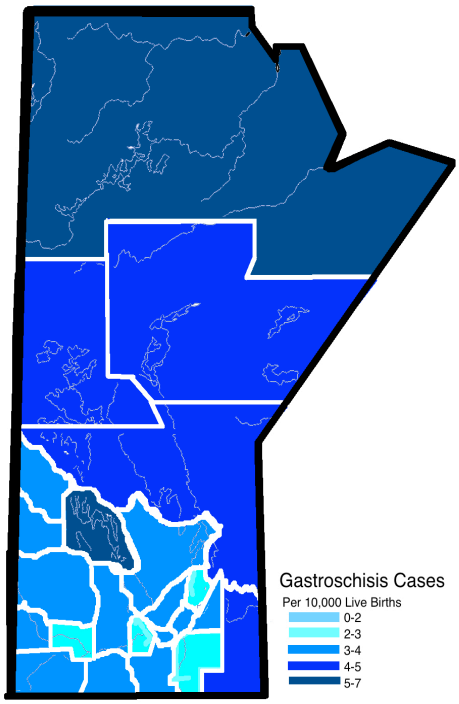

Figure 1: Spatial Distribution of gastroschisis cases in Manitoba by census division from 2009-2014.

Discussion

GS research is continuing to grow with the defect's exact aetiology still being unclear (14) with prevalence rates increasing in certain American states (2,9), in the United States (8), Canada (4), and worldwide (4,6). GS hot spots have been an area of interest of previous studies (31,32) and are an important phenomena requiring further study. This study not only adds to the previously existing body of research pertaining to GS, but has identified a new hot spot specific to Canada and more specifically to Manitoba. The concept of congenital abnormality hot spots is not only of interest from a Public Health prospective, but can begin to allow researchers the opportunity to further characterize this malformation.

Our results suggest there is a GS hot spot in the Northern region of Manitoba. There is a 2 to 3 fold increase in prevalence in these regions as compared to Southern Manitoba. Specific analysis of this population was not within the objectives of this primary analysis, however, further subgroup analysis needs to be performed to further identify possible mechanisms to explain the increased prevalence in northern Manitoba versus sourthern Manitoba, the Interlake region and Winnipeg.

As repeatedly described in the literature, it is thought that the aetiology of GS is complex and multifactorial (3,5,7,14,16,32). It is thought that that environmental factors such as smoking during pregnancy (2,14,17–20), use of OTC medications such as ASA (19,21), periconceptual alcohol consumption (23), use of cocaine, methamphetamines or ecstasy (19), and maternal exposure to surface water atrazine and spring conception (24) may play a role in the vascular compromise in

utero leading to the abdominal wall defect. Whereas some maternal characteristics such as young maternal age(2,8,13–16), primigravida status (2), first trimester maternal stress (25), use of any antidepressant during pregnancy (14), maternal history of pre-gestational diabetes mellitus 1 or 2 (14), history of gynaecological disease (19) and pre-conceptual or first trimester genitourinary infections (26) may also contribute.

An ethnicity component has also been suggested with GS being frequently observed in young, Aboriginal, smoking mothers in a Canadian study (30) while various American studies suggest higher rates in Hawaiian, Guamanian, American Indian, Native Alaskan, Samoan women (28), mothers who are US born versus non-US born (15) and teenage mothers who were White versus Black (29).

We can hypothesize that the GS hot spot identified in this study is also a complex multifactorial process. We may also postulate that the region of Northern Manitoba itself and the characteristics it possesses may further contribute to the observed increased prevalence.

According to *Volume 3; Population Groups and Ethnic Origins*, a document that comprises information from Statistics Canada 2001 and 2006 Censuses on Manitoba's population groups according to visible and non-visible minority self-identification, the total population of Manitoba was 1,133,515 with a North American Indian population of 120,415, or 10.6%, in 2006 (33). North American Indian is considered an Aboriginal group along with Metis, Inuit and refers to Aboriginal identity (34). For the remainder of this discussion, the term Aboriginal

will be used when describing North American Indians, Metis, Inuits XXXX for simplicity.

This report divided Manitoba into 7 regions; Winnipeg, Eastern, Central, Western, Interlake, Parklands and Norman. The Norman region consists of all land north of Le Pas, Grand Rapids, Fisher River and Blood Vein (33). The Norman region corresponds with the location of the identified GS hot spot.

As per the report, the Norman region has a total population of 67,990 consisting of the largest number of Aboriginals at 41,900 (61.6%). That is, 34.7% of the total Aboriginal Population of Manitoba (33). The second largest number of Aboriginals was identified in the Winnipeg region with a population of 34, 525, 5.5% of the total population of that region (n=625,705), and 28.7% of total Aboriginal population (33).

Lastly, the Interlake region had a total population of 77,370 and a Aboriginal population of 11,050, 14.3% of the total population of that region and 9.2 % of all Aboriginals (33).

Another report also explains that in 2006 the majority of Manitobans living in the North Economic Region (census Division 19, 21, 22, 23) were Aboriginal. The census Divisions19, 21, 22, 23 overlaps almost exclusively with the previously described Norman region (34,35). It can be concluded that there is in fact a distinctive population that resides in the Northern communities of Manitoba where we have identified a GS hot spot.

The *Aboriginal People in Manitoba* is a report produced from Manitoba Government Program and Statistics Canada 2006 Census data which provides

information about Aboriginal people in Manitoba (34). As we have suggested, there is a unique population residing in what we have identified as a GS hot spot, that being Aboriginals. This report highlighted risks factors previously identified as being contributors for GS. These may relate to the phenomenon of the increase regional prevalence of GS and perhaps may also provide clues to further understanding the etiology of GS.

Risk factors for new births in Manitoba for Aboriginals from 2003-2009 were compiled and showed notable results. Specifically, Aboriginal mothers were up to five times more likely to be a teenage mother at first birth, a lone parent, suffer from maternal depression, be socially isolated, smoke during pregnancy, drink alcohol during pregnancy, suffer from relationship distress and have a high birth weight (34,36). More specifically, maternal smoking during pregnancy was 56.5% in 2003 and dropped to 53.7% in 2009 (34).

It is well known that income levels are strongly predictive of the health and well being (34). Low-income predisposes to material and social deprivations which in turn leaves individuals unable to afford adequate food, clothing, and housing (37). It has been reported that income rate for Aboriginal females is almost twice as low when compared to Aboriginal men. Although dropping, the incidence for women was 31% to 17.9% compared to 23.1% to 9.2% for men (34). Furthermore, Mikkonen et al. describe that that dietary defficiencies are seen in food insecure homes and are assocaited with chronic disease as well as an increased incidence of cardiovascular disease, diabetes, hypertension and food-allergies(37).

As we have suggested, some risk factors exist in the Northern Manitoba region as it pertains Aboriginal people and may contribute to the observed increased prevalence of GS, however others may be protective. Increased BMI is thought to be protective for GS, (17) conversely there appears to be a significant numbers of individuals having increased BMI in these populations. It was reported that 75% of on-reserve Aboriginals were either overweight (35%) or obese (40%) and that 41% of youth (22%overweight; 19% obese) and 65% of children (53%overweight; 12%) (34) also carried increased BMIs.

There are significant risk factors associated with GS which may be overrepresented in the Northern populations. We postulate this may being a possible mechanism explaining the hot spot. Strong risk factors associated with GS exist, specifically; young maternal age and maternal tobacco exposure. Additionally, as women are earing less income they are in turn less likely to be eating healthy contributing to maternal malnutrition and chronic diseases such as diabetes which have both been suggested risk factors for GS (14,18). Conversely, this population also possesses a significant amount of a protective factor for GS, and increased BMI.

Our study addresses a new and important gap in the pre-existing literature. Although previous studies have successfully identified GS hot spots and thoroughly investigated the groups with precise data analysis (31,32), they are American studies. This study is this first of its kind in that it is specific to Canadian data and looks at Manitoba exclusively. Canada, and Manitoba more specifically, has a unique population distribution, healthcare system and challenges unique to its population.

Moreover, as we have identified another hot spot, we can begin to postulate possible explanations for such results and conduct future research.

One of the constraints of our study is a small sample size secondary to the low prevalence and time period examined in this province. Areas for future research include further characterization of specific maternal characteristics and environmental risk factors such as maternal age, maternal gravity, maternal tobacco, drug and alcohol use in these populations as have been identified in previous research (31,32). Furthermore, it would be of interest to examine the incidence of GS over a longer period of time and determine if the prevalence of GS in Northern Manitoba follows similar trends in increasing prevalence as seen in certain American states (2,9), in the United States (8), Canada (4), and worldwide (4,6). It would also be of interest to investigate if other GS hot spots exist in Canada or other countries and to attempt to further characterize the aetiology of the defect to determine if there are similar risks factors that can be identified with larger study pools. Thus, providing areas where interventional strategies can be implemented to potentially reduce the increasing rates of GS.

Conclusion

The increased incidence of GS is alarming and we still do not fully comprehend the etiology of this "hot spot". We have identified "hot spots" in Manitoba where there is a demonstrable increase in prevalence of GS. Although many of the clearly identified risk factors are present in these populations, they may possess additional characteristics that predispose these regions to an increased

prevalence of this structural developmental defect. It raises many questions upon which to build possible future research, interventions and prevention strategies to address this issue.

Acknowledgments

Thank you to the MPAS faculty, Dr. Michael Narvey, Dr. Chelsea Ruth and my supportive family and friends. Special thank you to my mentor Dr. Melanie Morris for her mentorship, patience and expertise.

References

1. Kelly KB, Ponsky T a. Pediatric abdominal wall defects. Surg Clin North Am [Internet]. Elsevier Inc; 2013;93(5):1255–67. Available from: http://dx.doi.org/10.1016/j.suc.2013.06.016

2. Hougland KT, Hanna AM, Meyers R, Null D. Increasing prevalence of gastroschisis in Utah. J Pediatr Surg. 2005;40:535–40.

3. Torfs CP, Christianson RE, Iovannisci DM, Shaw GM, Lammer EJ. Selected gene polymorphisms and their interaction with maternal smoking, as risk factors for gastroschisis. Birth Defects Res Part A - Clin Mol Teratol. 2006;76(October):723–30.

4. Moore A, Rouleau J SE. Chapter 7: Gastroschisis. In: Public Health Agency of Canada. Congenital anomalies in Canada 2013: a perinatal health surveillance report. [Internet]. Ottowa, Canada: Public Helath Agency of Canada; 2013. 57-64 p. Available from: http://publications.gc.ca/site/eng/443924/publication.html

5. Curry JI, McKinney P, Thornton JG, Stringer MD. The aetiology of gastroschisis. BJOG. 2000;107(November):1339–46.

6. Castilla EE, Mastroiacovo P, Orioli IM. Gastroschisis: International epidemiology and public health perspectives. Am J Med Genet Part C Semin Med Genet. 2008;148:162–79.

7. Moore A, Rouleau J SE. Congenital Anomalies in Canada 2013 a Perinatal Health Surveillance Report [Internet]. 2013. Available from: http://publications.gc.ca/site/eng/443924/publication.html

8. Kirby RS, Marshall J, Tanner JP, Salemi JL, Feldkamp ML, Marengo L, et al. Prevalence and correlates of gastroschisis in 15 states, 1995 to 2005. Obstet Gynecol [Internet]. 2013;122(2):275–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23969795

9. Langlois PH, Mareng LK CM. Time trends in the prevalence of birth defects in Texas 1999-2007: real or artifactual? Birth Defects Res A Clin Mol Teratol. 2011;91(10):902–17.

10. Laughon M, Meyer R, Bose C et al. Rising birth prevalence of gastroschisis. J Perinatol. 2003;23(4):291–3.35.

11. Chalmers J, Forrest J, Cant B HM. Congenital anterior abdominal wall defects—Rate of abdominal wall defects is higher in Scotland than in England and Wales. BMJ. 1997;314:371–2.

12. Calzolari E, Bianchi F, Dolk H MM 1995. Omphalocele and gastroschisis in Europe: A survey of 3 million births 1980–1990. EUROCAT Work Group Am J Med Genet. 1995;58(187-194).

13. Holland AJ a, Walker K, Badawi N. Gastroschisis: An update. Pediatr Surg Int. 2010;26:871–8.

14. Skarsgard ED, Meaney C, Bassil K, Brindle M, Arbour L, Moineddin R. Maternal risk factors for gastroschisis in Canada. Birth Defects Res Part A Clin Mol Teratol [Internet]. 2015;n/a – n/a. Available from: http://doi.wiley.com/10.1002/bdra.23349

15. Salemi JL, Pierre M, Tanner JP, Kornosky JL, Hauser KW, Kirby RS, et al. Maternal nativity as a risk factor for gastroschisis: A population-based study. Birth Defects Res Part A - Clin Mol Teratol. 2009;85(July):890–6.

16. Rasmussen S a., Frías JL. Non-genetic risk factors for gastroschisis. Am J Med Genet Part C Semin Med Genet. 2008;148:199–212.

17. Paranjothy S, Broughton H, Evans A, Huddart S, Drayton M, Jefferson R, et al. The role of maternal nutrition in the aetiology of gastroschisis: An incident case-control study. Int J Epidemiol. 2012;41(July):1141–52.

18. Lam PK, Torfs CP. Interaction between maternal smoking and malnutrition in infant risk of gastroschisis. Birth Defects Res Part A - Clin Mol Teratol. 2006;76(February):182–6.

19. Draper ES, Rankin J, Tonks AM, Abrams KR, Field DJ, Clarke M, et al. Recreational drug use: A major risk factor for gastroschisis? Am J Epidemiol. 2008;167(4):485–91.

20. Feldkamp ML, Alder SC, Carey JC. A case control population-based study investigating smoking as a risk factor for gastroschisis in Utah, 1997-2005. Birth Defects Res Part A - Clin Mol Teratol. 2008;82(November):768–75.

21. M.werler M, Sheehan JE, Mitchell A a. Maternal medication use and risks of gastroschisis and small intestinal atresia. Am J Epidemiol. 2002;155(1):26–31.

22. Mac Bird T, Robbins JM, Druschel C, Cleves M a., Yang S, Hobbs C a. Demographic and environmental risk factors for gastroschisis and omphalocele in the National Birth Defects Prevention Study. J Pediatr Surg [Internet]. Elsevier Inc.; 2009;44(8):1546–51. Available from: http://dx.doi.org/10.1016/j.jpedsurg.2008.10.109

23. Richardson S, Browne ML, Rasmussen S a., Druschel CM, Sun L, Jabs EW, et al. Associations between periconceptional alcohol consumption and craniosynostosis,

omphalocele, and gastroschisis. Birth Defects Res Part A - Clin Mol Teratol. 2011;91(May):623–30.

24. Waller S a., Paul K, Peterson SE, Hitti J. Agricultural-related chemical exposures, season of conception, and risk of gastroschisis in Washington State (American Journal of Obstetrics and Gynecology (2010) 202, 3, (241.e1-6)). Am J Obstet Gynecol [Internet]. Elsevier Inc.; 2010;203(3):183. Available from: http://dx.doi.org/10.1016/j.ajog.2010.01.023

25. Palmer SR, Evans A, Broughton H, Huddart S, Drayton M, Rankin J, et al. The role of maternal stress in early pregnancy in the aetiology of gastroschisis: An incident case control study. PLoS One. 2013;8(11):1–9.

26. Feldkamp M, Reefhuis J, Kucik J, Krikov S, Wilson A, Moore C, et al. Case-control study of self reported genitourinary infections and risk of gastroschisis: findings from the national birth defects prevention study, 1997-2003. BMJ. 2008;336:1420–3.

27. Akhtar J, Skarsgard ED. Associated malformations and the "hidden mortality" of gastroschisis. J Pediatr Surg [Internet]. Elsevier Inc.; 2012;47(5):911–6. Available from: http://dx.doi.org/10.1016/j.jpedsurg.2012.01.044

28. Rocha FG, Zalud I, Dye T. Ethnic variation of gastroschisis and omphalocele in the United States of America*. J Matern Neonatal Med [Internet]. 2014;27(14):1428–30. Available from: http://informahealthcare.com/doi/abs/10.3109/14767058.2013.876002

29. Williams LJ, Kucik JE, Alverson CJ, Olney RS, Correa A. Epidemiology of gastroschisis in Metropolitan Atlanta, 1968 through 2000. Birth Defects Res Part A - Clin Mol Teratol. 2005;73:177–83.

30. Brindle ME, Flageole H, Wales PW. Influence of maternal factors on health outcomes in gastroschisis: A canadian population-based study. Neonatology [Internet]. 2012;102(1):45–52. Available from: Available from ProQuest in http://link.worldcat.org/?rft.institution_id=129797&spage=45&pkgName=nhshospital&PQUEST.WAYFlessID=48693&issn=1661-7800&linkclass=to_article&jKey=38719&issue=1&provider=PQUEST&date=2012-06&aulast=Brindle+M.E.&atitle=Influence+of

31. Yazdy MM, Werler MM, Anderka M, Langlois PH, Vieira VM. Spatial analysis of gastroschisis in Massachusetts and Texas. Ann Epidemiol [Internet]. Elsevier Inc; 2015;25(1):7–14. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1047279714004396

32. Root ED, Meyer RE, Emch ME. Evidence of localized clustering of gastroschisis births in North Carolina, 1999-2004. Soc Sci Med [Internet]. Elsevier Ltd;

2009;68(8):1361–7. Available from: http://dx.doi.org/10.1016/j.socscimed.2009.01.034

33. Immigration MM and. Population Groups and Ethnic Origins [Internet]. 2009. Available from: https://www.gov.mb.ca/labour/immigration/pdf/manitoba-immigration-ethnicity-series-3.pdf

34. Government of Manitoba. Aboriginal People in Manitoba [Internet]. 2006. Available from: http://www.gov.mb.ca/ana/pdf/pubs/apm2006.pdf

35. Canada. S. 2011 Census divisions, 2011 Divisions de recensement [Internet]. 2011. Available from: http://www12.statcan.gc.ca/census-recensement/2011/geo/map-carte/pdf/2011-12572-01-A.pdf

36. Manitoab Healthy Child. Being Born and Starting School in Manitoba: The Families First Screening (FFS) and the Early Development Instrument (EDI). 2010; Available from: www.gov.mb.ca/healthychild/ncd/ncd2010_santos_pre.pdf

37. Mikkonen J, Raphael D. Social Determinants of Health: The Canadian Facts [Internet]. 2010. 62 p. Available from: http://www.thecanadianfacts.org