GASTROSCHISIS IN FINLAND 1993 – 2014. INCREASING PREVALENCE, HIGH RATES OF ABORTION AND SURVIVAL

A population-based study

Arimatias Raitio[1], Asta Lahtinen[2], Johanna Syvänen[1], Teemu Kemppainen[3], Eliisa Löyttyniemi[3], Mika Gissler[4,5], Anna Hyvärinen[6], Ilkka Helenius[1]

1. Department of Paediatric Surgery and Orthopaedics, University of Turku and Turku University Hospital, Turku, Finland
2. Department of Paediatric Surgery, Kuopio University Hospital, Kuopio, Finland
3. Department of Biostatistics, University of Turku and Turku University Hospital, Turku, Finland
4. National Institute of Health and Welfare, Helsinki, Finland
5. Karolinska Institute, Department of Neurobiology, Care Sciences and Society, Stockholm, Sweden
6. Department of Paediatric Surgery, University of Tampere and Tampere University Hospital, Tampere, Finland

Abstract

Aim

To assess the changes in prevalence and mortality of gastroschisis, and to identify associated anomalies.

Material and Methods

A population-based nationwide study. All gastroschisis cases were identified in the Finnish Register of Congenital Malformations and the Care Register for Health Care from 1993 to 2014 including live births, stillbirths, and terminations of pregnancy due to fetal anomalies. Associated anomalies were recorded, and analyzed, and prevalence and infant mortality were calculated.

Results

There were 320 cases of gastroschisis; 235 (73%) live births, 16 (5%) stillbirths and 69 (22%) terminations of pregnancy. Live birth prevalence of gastroschisis in Finland was lower than generally reported (1.73 in 10,000). However, due to relatively high rates of abortion, our total prevalence of 2.57/10,000 was similar with other reports. The most common risk factor was young maternal age. Babies with gastroschisis were born prematurely, on average on the 36th week and most are delivered by Caesarean section. There was a significant increasing trend in live birth prevalence (p=0.0018). Overall infant mortality was 7.7% (18/235); 7.2% (16/222) in simple gastroschisis and 15% (2/13) in complex gastroschisis. Associated anomalies were rare both in aborted fetuses and neonates, and there was only one case with a chromosomal abnormality.

Conclusion

Gastroschisis is usually an isolated anomaly with increasing birth prevalence and excellent survival rates. Regardless of the good prognosis, the abortion rates in Finland are higher than previously reported, and we hypothesize this to be due to lack of appropriate antenatal counselling.

Keywords: gastroschisis, prevalence, abortion

Introduction

Gastroschisis is an open abdominal wall defect lateral to the umbilical cord, and in most cases, an isolated anomaly. Complex gastroschisis with bowel damage or obstruction occurs in approximately 13-20 % of cases.[1,2] Up to one third of gastroschisis patients have associated anomalies and cardiac defects are reported in up to 10 % of cases.[3-5] Gastroschisis occurs in 2.1-5.3 per 10 000 live births.[2,6-8] For reasons unknown, the worldwide birth prevalence of gastroschisis has increased dramatically over the last decades, but these studies have lacked the total prevalence.[2,7,8] The most consistent risk factor for gastroschisis is young maternal age, but interestingly the incidence is increasing in all age groups, not only in younger women.[9-12]

In general, over 90% of the gastroschisis cases are detected in prenatal ultrasound screening.[6,13] Pregnancies affected by gastroschisis are often more complicated and intrauterine fetal demise occurs in 2.5-15%.[6,14,15] Infants with gastroschisis tend to be slightly preterm and are born on 36 weeks on average.[16,17] Although the majority are born through caesarean section, evidence does not associate the mode of delivery with mortality.[18,19] Once born, these infants require surgical intervention shortly after birth. When appropriate obstetric and neonatal care are provided, the overall survival rates are above 90%.[2,7,20-22] Regardless of the low mortality, gastroschisis often requires lengthy hospitalization especially in the complex cases.[2,23] Due to the associated morbidity, up to 14% of the families opt for termination of pregnancy.[6,15,24]

The aim of this study was to assess the changes in prevalence, mortality and abortion rates of gastroschisis in the Finnish population, and additionally to identify the most commonly associated anomalies and risk factors for mortality.

Methods

The data were collected from the Finnish Register of Congenital Malformations, which contains data on all live births, stillbirths, and terminations of pregnancy due to severe fetal anomalies. This registry has been maintained by the National Institute for Health and Welfare since 1963 and it also receives information from other national health registers (the Medical Birth Register, the Register of Induced Abortions, the Care Register for Health Care, and the Register of Visual Impairment and National Hospital Discharge Register) and the Cause of Death statistics collected by Statistics Finland. The main purpose of the national register is to monitor prevalence of congenital anomalies and to allow early detection of their potential risk factors.

As the “Declaration of Malformation” forms are received from the maternity and paediatric hospitals, the list of diagnosis is obtained and confirmed with the previously mentioned registries and additional information (patient records, radiographs, photographs, specialist consultation etc.) is requested if deemed necessary before entering the data to the register. All recorded diagnosis are evaluated, classified, coded and double-checked by a medical geneticist and the coverage and data quality of the register have been considered good in several studies.[25,26] As required by the national legislation, the

use of the data was authorized by the National Institute of Health and Welfare after consulting the data protection authority.

The diagnoses are coded according to the International Classification of Diseases (ICD) by the World Health Organization – both ninth and tenth revisions (ICD-9 and ICD-10) were used during our study period from 1993 to 2014. For our analysis, we searched the register for all the cases with codes either 756.73 (ICD-9) or Q79.3 (ICD-10) for gastroschisis and included them in the study. The first three years of our study period contains information only on the live births, as the data on stillbirths and terminations of pregnancy became available in 1997. Cases associated with bowel atresia, bowel necrosis, perforation, and/or volvulus were classified as complex gastroschisis.

All risk factors were evaluated with chi-square test or Fisher's exact test. The average age of mothers who had a child with gastroschisis was compared with the average age of all mothers who have given birth in Finland with one sample t-test. The change in live birth prevalence during our study period was evaluated with linear regression. All statistical tests were performed as two-sided, with a significance level set at $p<0.05$. The analyses were performed using SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). Birth prevalence and total prevalence are given per 10 000 births, and live birth prevalence is given per 10 000 live births as defined by EUROCAT.[27]

Results

We identified 320 gastroschisis cases from 1993 to 2014 in Finland. There were 235 (73.4%) live births, 16 (6.4%) stillbirths and 69 (21.6%) of the families opted for the termination of pregnancy. Total prevalence of gastroschisis including live births, stillbirths and abortions due to anomalies was 2.57 per 10,000 births. Birth prevalence (live births and stillbirths) was 1.85/10,000 and live birth prevalence was 1.73 per 10,000 live births. There was a significant increase in live birth prevalence of gastroschisis from 1993 to 2014 ($p=0.0018$) – Figure 1. Similar, yet statistically not significant, trend was also observed in the total prevalence ($p=0.29$) – Figure 2. The number of stillbirths and abortions remained constant.

The majority were born slightly preterm, on 36th week on average. Caesarean section (N=146, 58%) was more common than vaginal delivery (N=105, 42%). The average age of mothers in Finland rose during our study period from 29.3 to 30.6 years. Gastroschisis was significantly associated with lower than average maternal age (mean 24.3 [SD 4.6] years vs 30.0 years, $p<0.001$).

Gastroschisis was rarely associated with other birth defects. There was only one chromosomal abnormality (Turner's syndrome) in our series and that pregnancy was terminated. Among the aborted fetuses, 7% (5/69) had central nervous system malformations, 1% (1/69) had urogenital, and 1% (1/69) had skeletal abnormalities.

Congenital heart defects were found in 4% (9/251) of those who were born. So called complex gastroschisis with bowel compromise and/or atresia occurred in 5% (13/251) of these infants.

Additionally, one case of each of the following major anomalies was found: cleft lip and palate, central nervous system defect, urogenital malformation, congenital diaphragmatic hernia and craniosynostosis. Furthermore, there were problems related to preterm birth as 25% (62/251) were born prematurely including intracerebral hemorrhages (3%, 7/251), pulmonary hypertension (1%, 2/251), and one case of pneumothorax.

Infant mortality of gastroschisis was low, 7.7% (18/235). Simple gastroschisis had slightly lower mortality, 7.2% (16/222) while complex cases with bowel compromise and/or atresia had higher mortality (15%, 2/13). The mode of delivery had no impact on mortality; vaginal and caesarean delivery were associated with 9% (8/80) and 7% (10/136) infant mortality respectively (p=0.61). Maternal smoking was associated with slightly elevated mortality (10% [7/59] vs 7% [11/146] in non-smokers) but the difference was not statistically significant (p=0.42). Maternal obesity (BMI≥30), diabetes, and hypertension had no impact on infant mortality. Interestingly, mothers who opted for the termination of pregnancy were significantly older than those who decided to continue their pregnancy (mean age 28.8 [SD 6.4] years vs 24.3 [SD 4.6] years, p<0.001).

Discussion

Several studies have reported worldwide increase in the prevalence of gastroschisis from the 1980s and according to recent reports the increasing trend has continued.[2,8,18,28] Similarly in our cohort, there was a marked increasing trend in the live birth prevalence. Additionally, a previous population-based study in Finland showed a significant increase in birth prevalence of gastroschisis from 0.77 to 1.42 per 10,000 during the 1970s.[29] Hence, there has also been a substantial increase from the 1970s to our total prevalence of 2.57 per 10,000 births, which is best comparable with earlier numbers from the era before abortions for fetal anomalies.

Even though the increasing prevalence of gastroschisis is a worldwide phenomenon, no clear explanation has been found. Several risk factors of gastroschisis have been previously identified and we speculate that altered exposure may affect the prevalence. The use of recreational drugs, a known risk factor for gastroschisis[30], has increased in Finland since 1992.[31] Similarly, there has been a marked increase in genital herpes infections since 1970s.[32] The infection itself and/or the antiherpetic drugs are associated with higher risk of gastroschisis.[33] Also, short length of sexual cohabitation appears to be associated with elevated risk[34] which could explain the increased prevalence as the number of blended families has been on steady increase in Finland since the 1990s.[35] Smoking, on the other hand, which is associated with increased risk of gastroschisis[30,36], has been on steady decrease in Finland since the end of 1980s.[37]

Infant mortality of gastroschisis was 7.7%, in keeping with previous reports.[16-18,20-22] However, recent reports from the US have shown mortality rates <5% with no statistical difference between simple and complex cases.[2,7] In our series, mortality was substantially higher for complex gastroschisis (15% vs

7.2%). Nevertheless, it did not reach statistical significance (p=0.26). Several risk factors for infant mortality have been identified including maternal obesity, smoking and diabetes. We found no statistical correlation with these risk factors and mortality. However, this may be due to limited sample size. Proportion of stillbirths was 6% and in range with previous reports (2.5-15%).[14,15,38]

According to some studies, up to one third of gastroschisis cases may have other associated anomalies including cardiac defects.[3-5] Bowel compromise due to necrosis, volvulus or atresia is seen in 13-20% of cases.[1,2] In our study population, however, complex gastroschisis occurred in 5% and only 4% had heart defects. Our data were concordant with previous studies confirming that in most cases gastroschisis is an isolated anomaly.[2,15,18]

High rates of prenatal detection of gastroschisis allows planning and selecting the optimal mode of delivery. Both in our series and in other reports, most of these infants are born with Caesarean section.[18,19] However, recent studies have shown no evidence of the benefits of caesarean section on clinical outcomes such as mortality, sepsis, primary repair, duration of parenteral feeding and hospital stay.[19,39] Furthermore, there is limited evidence of the association of Caesarean delivery and adverse clinical outcomes.[15] However, as the authors hypothesized, this may be a reflection of the indications for the Caesarean section rather than the procedure itself. As a large number of studies have not supported the benefits of performing Caesarean section, it is evident that unnecessary Caesarean deliveries are common among these neonates.

There are regional differences in abortion rates and practices related to culture, religion and legislation. One Canadian cohort had no abortions in their series, but in general, the termination rates for antenatally detected gastroschisis vary from 5 to 14%. [6,15,24] In our series 22% of the gastroschisis cases were abortions. If those not found in prenatal screening had been excluded, the proportion of families opting for abortion would have been even higher. To the best of our knowledge this is the highest termination rate reported. This is a controversial finding as gastroschisis in Finland has low mortality and proportion of complex cases with additional anomalies is low. We hypothesize that this may be due to insufficient antenatal counselling.

The strength of our study was the use of high-quality register data with total population coverage. The main limitations are a relatively small sample size and that this study solely relies on the accuracy of register data.

In conclusion, gastroschisis is more common in younger mothers and the increasing prevalence appears to be a worldwide phenomenon. Changes in certain risk factors may explain the increasing trend. Elective terminations are common in Finland regardless of the good prognosis and scarcity of associated anomalies.

Acknowledgements

The author's research leave and statistician's salary were funded by grants from the Clinical Research Institute HUCH.

Conflict of Interest

None.

References

1. Bergholz R, Boettcher M, Reinshagen K, Wenke K. Complex gastroschisis is a different entity to simple gastroschisis affecting morbidity and mortality-a systematic review and meta-analysis. *J Pediatr Surg*. 2014;49(10):1527-1532.

2. Bhatt P, Lekshminarayanan A, Donda K, et al. Trends in incidence and outcomes of gastroschisis in the united states: Analysis of the national inpatient sample 2010-2014. *Pediatr Surg Int*. 2018;34(9):919-929.

3. Garne E, Loane M, Dolk H, et al. Prenatal diagnosis of severe structural congenital malformations in europe. *Ultrasound Obstet Gynecol*. 2005;25(1):6-11.

4. Benjamin B, Wilson GN. Registry analysis supports different mechanisms for gastroschisis and omphalocele within shared developmental fields. *Am J Med Genet A*. 2015;167A(11):2568-2581.

5. Akhtar J, Skarsgard ED, Canadian Pediatric Surgery Network (CAPSNet). Associated malformations and the "hidden mortality" of gastroschisis. *J Pediatr Surg*. 2012;47(5):911-916.

6. Fleurke-Rozema H, van de Kamp K, Bakker M, Pajkrt E, Bilardo C, Snijders R. Prevalence, timing of diagnosis and pregnancy outcome of abdominal wall defects after the introduction of a national prenatal screening program. *Prenat Diagn*. 2017;37(4):383-388.

7. Anderson JE, Galganski LA, Cheng Y, et al. Epidemiology of gastroschisis: A population-based study in california from 1995 to 2012. *J Pediatr Surg*. 2018;53(12):2399-2403.

8. Castilla EE, Mastroiacovo P, Orioli IM. Gastroschisis: International epidemiology and public health perspectives. *Am J Med Genet C Semin Med Genet*. 2008;148C(3):162-179.

9. Robledo-Aceves M, Bobadilla-Morales L, Mellin-Sanchez EL, et al. Prevalence and risk factors for gastroschisis in a public hospital from west mexico. *Congenit Anom (Kyoto)*. 2015;55(2):73-80.

10. Chabra S, Gleason CA, Seidel K, Williams MA. Rising prevalence of gastroschisis in washington state. *J Toxicol Environ Health A*. 2011;74(5):336-345.

11. Vu LT, Nobuhara KK, Laurent C, Shaw GM. Increasing prevalence of gastroschisis: Population-based study in california. *J Pediatr*. 2008;152(6):807-811.

12. Loane M, Dolk H, Bradbury I, EUROCAT Working Group. Increasing prevalence of gastroschisis in europe 1980-2002: A phenomenon restricted to younger mothers? *Paediatr Perinat Epidemiol*. 2007;21(4):363-369.

13. Rossi AC, Prefumo F. Accuracy of ultrasonography at 11-14 weeks of gestation for detection of fetal structural anomalies: A systematic review. *Obstet Gynecol*. 2013;122(6):1160-1167.

14. Brantberg A, Blaas HG, Salvesen KA, Haugen SE, Eik-Nes SH. Surveillance and outcome of fetuses with gastroschisis. *Ultrasound Obstet Gynecol*. 2004;23(1):4-13.

15. Nicholas SS, Stamilio DM, Dicke JM, Gray DL, Macones GA, Odibo AO. Predicting adverse neonatal outcomes in fetuses with abdominal wall defects using prenatal risk factors. *Am J Obstet Gynecol*. 2009;201(4):383.e1-383.e6.

16. Overcash RT, DeUgarte DA, Stephenson ML, et al. Factors associated with gastroschisis outcomes. *Obstet Gynecol*. 2014;124(3):551-557.

17. Brindle ME, Flageole H, Wales PW, Canadian Pediatric Surgery Network (CAPSNet). Influence of maternal factors on health outcomes in gastroschisis: A canadian population-based study. *Neonatology*. 2012;102(1):45-52.

18. Brebner A, Czuzoj-Shulman N, Abenhaim HA. Prevalence and predictors of mortality in gastroschisis: A population-based study of 4803 cases in the USA. *J Matern Fetal Neonatal Med*. 2018:1-7.

19. Lopez A, Benjamin RH, Raut JR, et al. Mode of delivery and mortality among neonates with gastroschisis: A population-based cohort in texas. *Paediatr Perinat Epidemiol*. 2019;33(3):204-212.

20. Lao OB, Larison C, Garrison MM, Waldhausen JH, Goldin AB. Outcomes in neonates with gastroschisis in U.S. children's hospitals. *Am J Perinatol*. 2010;27(1):97-101.

21. Owen A, Marven S, Johnson P, et al. Gastroschisis: A national cohort study to describe contemporary surgical strategies and outcomes. *J Pediatr Surg*. 2010;45(9):1808-1816.

22. Cowan KN, Puligandla PS, Laberge JM, et al. The gastroschisis prognostic score: Reliable outcome prediction in gastroschisis. *J Pediatr Surg*. 2012;47(6):1111-1117.

23. Keys C, Drewett M, Burge DM. Gastroschisis: The cost of an epidemic. *J Pediatr Surg*. 2008;43(4):654-657.

24. Ekin A, Gezer C, Taner CE, et al. Fetal abdominal wall defects: Six years experience at a tertiary center. *Clin Exp Obstet Gynecol*. 2015;42(3):327-330.

25. Greenlees R, Neville A, Addor MC, et al. Paper 6: EUROCAT member registries: Organization and activities. *Birth Defects Res A Clin Mol Teratol*. 2011;91 Suppl 1:S51-S100.

26. The finnish register of congenital malformations. national institute for health and welfare. http://Www.thl.fi/en_US/web/en/statistics/topics/reproductive_health/congenital_anomalies. accessed 2014 jul 10. .

27. European surveillance of congenital anomalies. www.eurocat-network.eu. accessed 2014 jul 10. .

28. Jones AM, Isenburg J, Salemi JL, et al. Increasing prevalence of gastroschisis--14 states, 1995-2012. *MMWR Morb Mortal Wkly Rep*. 2016;65(2):23-26.

29. Hemminki K, Saloniemi I, Kyyronen P, Kekomaki M. Gastroschisis and omphalocele in finland in the 1970s: Prevalence at birth and its correlates. *J Epidemiol Community Health*. 1982;36(4):289-293.

30. Draper ES, Rankin J, Tonks AM, et al. Recreational drug use: A major risk factor for gastroschisis? *Am J Epidemiol*. 2008;167(4):485-491.

31. Yearbook of alcohol and drug statistics 2018. http://Www.julkari.fi/handle/10024/137332. . 2018.

32. Vuorenmaa L, Ilola A, Mussalo-Rauhamaa H. Sukupuolitaudit suomessa – eilen, tänään ja huomenna. https://Www.avi.fi/documents/10191/149165/Sukupuolitaudit+Suomessa+eilen+tanaan+ja+huomenna/6d4060db-df05-4372-a4fc-6633b796fdb2. *Regional State Administrative Agency for Southern Finland*. 2012.

33. Ahrens KA, Anderka MT, Feldkamp ML, et al. Antiherpetic medication use and the risk of gastroschisis: Findings from the national birth defects prevention study, 1997-2007. *Paediatr Perinat Epidemiol*. 2013;27(4):340-345.

34. Rittler M, Castilla EE, Chambers C, Lopez-Camelo JS. Risk for gastroschisis in primigravidity, length of sexual cohabitation, and change in paternity. *Birth Defects Res A Clin Mol Teratol*. 2007;79(6):483-487.

35. Väisänen H, Helamaa T. The family federation of finland. https://Www.vaestoliitto.fi/tieto_ja_tutkimus/vaestontutkimuslaitos/tilastoja/perheet/uusperheet_suomessa/. . 2014.

36. Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: A systematic review based on 173 687 malformed cases and 11.7 million controls. *Hum Reprod Update*. 2011;17(5):589-604.

37. The finnish institute for health and welfare. http://Urn.fi/URN:NBN:Fi-fe2018102938947. . 2018.

38. South AP, Stutey KM, Meinzen-Derr J. Metaanalysis of the prevalence of intrauterine fetal death in gastroschisis. *Am J Obstet Gynecol*. 2013;209(2):114.e1-114.13.

39. Kirollos DW, Abdel-Latif ME. Mode of delivery and outcomes of infants with gastroschisis: A meta-analysis of observational studies. *Arch Dis Child Fetal Neonatal Ed*. 2018;103(4):F355-F363.

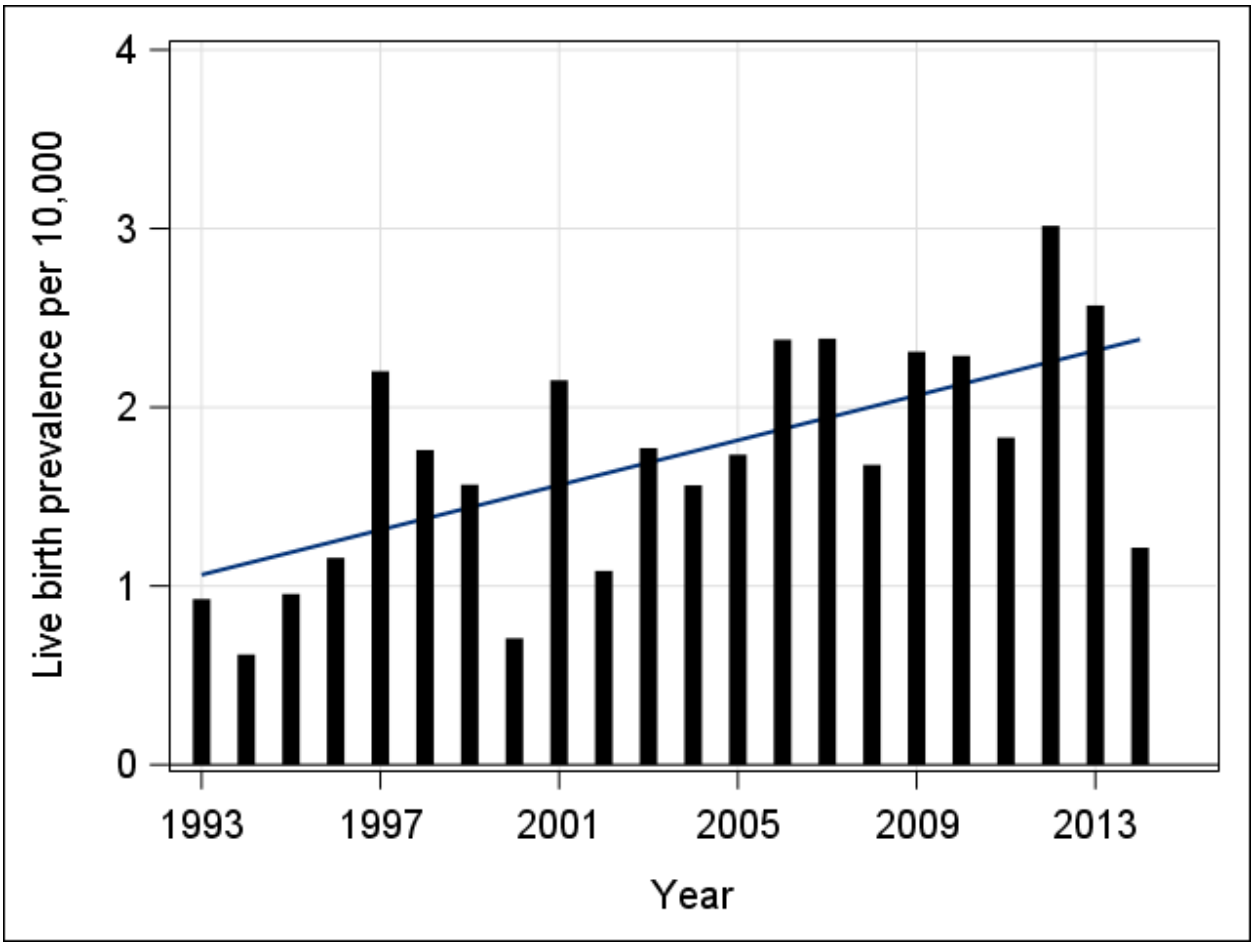

Figure 1. Increasing trend in live birth prevalence of gastroschisis. P=0.0018

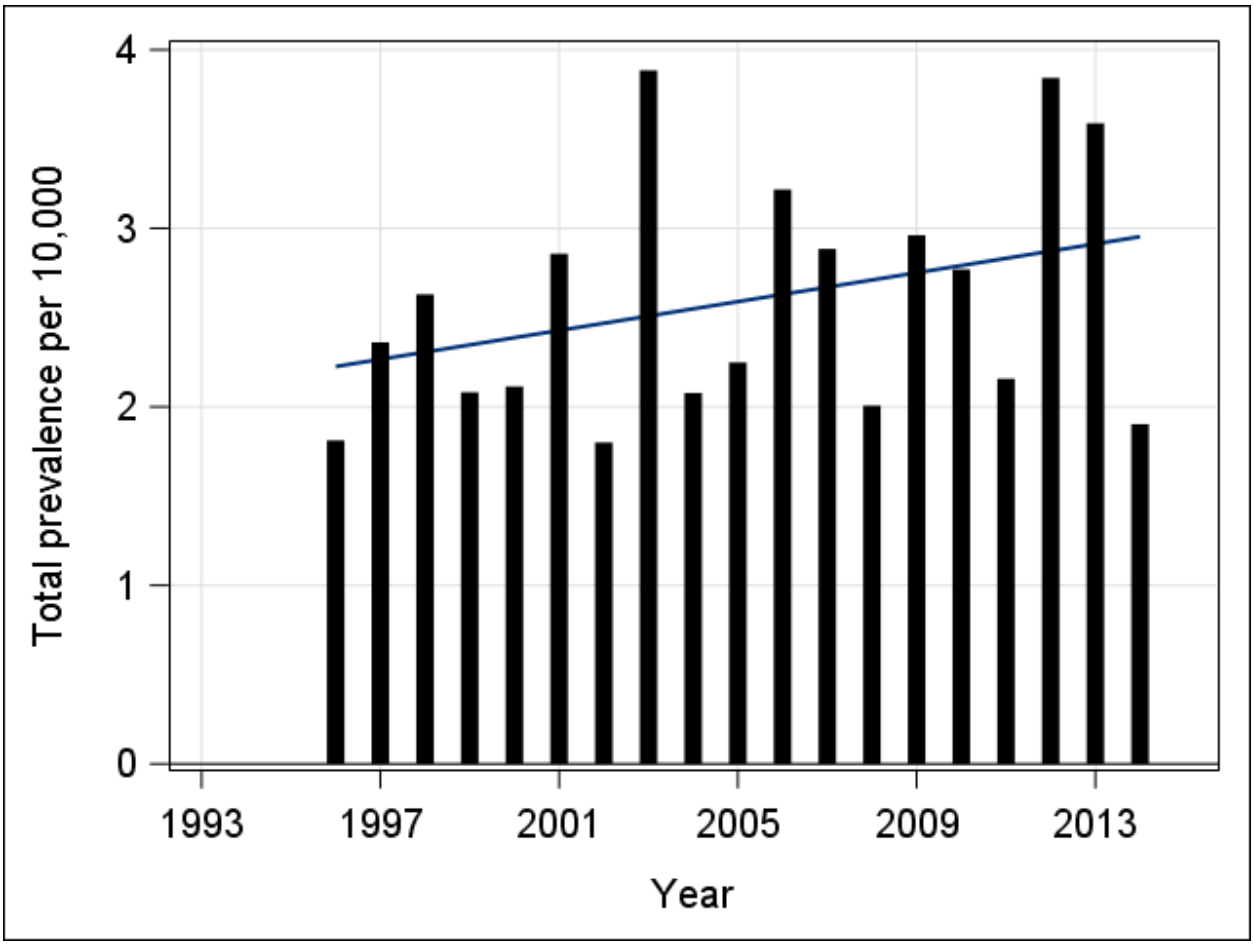

Figure 2. Increasing, yet not statistically significant, trend of total birth prevalence of gastroschisis. P=0.29