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RESEARCH ARTICLE

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Maternal risk factors for gastroschisis: A population-based case–control study

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Abstract

Background: Gastroschisis is an open abdominal wall defect with low mortality but significant morbidity. The prevalence has been increasing worldwide for the past decades. Several risk factors for gastroschisis have been identified, but no clear reason for increasing prevalence has been found. In our study, we aimed to assess and identify maternal risk factors for gastroschisis.

Methods: In our nationwide register-based case–control study, we identified all gastroschisis cases in the Finnish Register of Congenital Malformations from 2004 to 2014. Information on drug prescriptions and purchases was received from Drugs and Pregnancy database. Five healthy age-matched controls from the same geographical region were randomly selected for each case. Conditional logistic regression was used to evaluate different risk factors.

Results: One-hundred-eighty-eight cases of gastroschisis were identified and compared with 910 matched controls. Nulliparity was a significant risk factor for gastroschisis, aOR 2.00 (95% CI 1.29–3.11) whereas obesity was protective, aOR 0.35 (95% CI 0.15–0.83). Smoking appeared to increase the risk for gastroschisis, aOR 1.32 (95% CI 0.88–1.97). The mean maternal age of newborns with gastroschisis was significantly lower than average (p <.001).

Conclusion: As in previous studies, nulliparity and young maternal age were significant risk factors for gastroschisis. Maternal obesity significantly reduced the risk of gastroschisis regardless of maternal age and gestational diabetes.

KEYWORDS

gastroschisis, maternal risk factor, nulliparity, obesity, smoking

1 | INTRODUCTION

Gastroschisis is an open abdominal wall defect lateral to the umbilical cord. The pathogenesis is largely unknown, but most recent evidence suggests that gastroschisis is a primary midline malformation of the umbilical ring (Bargy & Beaudoin, 2014; Opitz, Feldkamp, & Botto, 2019; Rittler, Vauthay, & Mazzitelli, 2013) possibly a resulting from the rupture of the physiological hernia (Beaudoin, 2018). The critical susceptibility window

occurs in the first trimester of pregnancy (Feldkamp & Botto, 2008). The worldwide prevalence of gastroschisis has been increasing during the last decades; similarly in Finland (Anderson et al., 2020; Bhatt et al., 2018; Castilla, Mastroiacovo, & Orioli, 2008; Raitio et al., 2019). Several theories for this rise have been suggested including increased teen pregnancy, increased illicit substance abuse during pregnancy, and more frequent chemical exposures (Short et al., 2019; Souther, Puapong, Woo, & Johnson, 2017; Winchester, Huskins, & Ying, 2009). However, as there are multiple risk factors of gastroschisis, clear explanation for this increasing trend has not been found.

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 (Vu, Nobuhara, Laurent, & Shaw, 2008; Chabra, Gleason, Seidel, & Williams, 2011; Loane et al., 2007; Robledo-Aceves et al., 2015). Similarly, there is clear evidence that smoking and the use of recreational drugs during pregnancy increase the risk of gastroschisis (Draper et al., 2008; Hackshaw, Rodeck, & Boniface, 2011). Also environmental factors, especially pesticides, appear to be associated with elevated risk (Mattix, Winchester, & Scherer, 2007; Souther et al., 2017; Waller, Paul, Peterson, & Hitti, 2010). However, there are only a handful of studies on the effects of maternal medications with evidence that certain medications may also increase the risk (Ahrens et al., 2013; Anderson et al., 2020; Given et al., 2017; Werler, Guéry, Waller, & Parker, 2018; Werler, Sheehan, & Mitchell, 2002).

The aim of this study was to assess and identify potential maternal risk factors of gastroschisis, and especially to assess the effects of the medications used during the first trimester of pregnancy. We hypothesized, that maternal medication during the first trimester of pregnancy would affect the risk of gastroschisis.

2 | METHODS

The analysis is based on the records of the Finnish Register of Congenital Malformations, the Medical Birth Register, the Register on the Induced Abortions and the Care Register for Health Care, all maintained by the Finnish Institute for Health and Welfare. The data on maternal prescription medicine use was obtained from the Register on Reimbursed Drug Purchases upheld by the Finnish Social Insurance Institution (Kela) through Drugs and Pregnancy database. These data were limited to drug purchases in a time window of 1 month before conception and the first trimester of pregnancy. These registers receive information based on a legally compulsory announcement request on all health personnel in our country. The accuracy and high coverage of these data sources have been validated in multiple national and international investigations (Gissler, Teperi, Hemminki, & Meriläinen, 1995; Kela, 2019; Leoncini et al., 2010; Pakkasjärvi et al., 2006).

The diagnoses in the registers are coded according to the International Statistical Classification of Diseases and Health Related Problems by the World Health Organization (WHO). For our analysis, we searched the register for all the gastroschisis cases born between January 1, 2004 and December 31, 2014 and included them in the study. Five healthy controls from the Medical Birth Register matched for maternal age (± 1 year), residency, and time of conception (± 1 month) were randomly selected for each case. For the terminated fetuses, live-born, healthy controls were selected.

Maternal risk factors in the register were analyzed including BMI, parity, smoking, documented illnesses and history of miscarriages. Maternal diabetes group contained both type 1 and 2 diabetes diagnosed before conception. Gestational diabetes group included all women with recorded diagnosis of gestational diabetes or abnormal oral glucose tolerance result. Smoking was defined as active smoking during first trimester. Maternal weight was recorded at the first prenatal visit 8–10 weeks after conception. The initial analysis on maternal medication was done at the fourth level of the Anatomical Therapeutic Chemical (ATC) Classification System by WHO. Subsequently, we identified and selected those ATC groups with higher proportion of events among cases for further analysis.

Conditional logistic regression was used to evaluate different risk factors based on literature and data availability. First, univariate models were programmed, and Fisher's exact test was executed to search potential risk factors (Table 1). Subsequently, a multivariable model was created. Odds ratios (OR) along with adjusted odds ratios (aOR) with 95% confidence intervals (CI) were calculated. As a strong interaction was observed between maternal BMI and gestational diabetes ($p < .001$), we created new combination variables for multivariable models. The analyses were performed using SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC).

The approval of the Institutional Review boards at the Finnish Institute of Health and Welfare and Turku University Hospital were obtained before conducting this register study.

TABLE 1 Univariate analysis of the maternal risk factors for gastroschisis

	Number of events			
	Cases (n = 147–188)	Controls (n = 880–910)	Odds ratio	95% CI
Maternal obesity (BMI > 30)	7/147 (4.8%)	93/880 (10.6%)	0.39	0.16–0.91
Maternal underweight (BMI < 18.5)	10/147 (6.8%)	59/880 (6.7%)	0.89	0.43–1.85
Nulliparity	129/188 (68.6%)	536/910 (58.9%)	1.65	1.14–2.39
Smoking	52/150 (34.7%)	248/891 (27.8%)	1.35	0.92–1.99
Previous miscarriages	35/187 (18.7%)	137/910 (15.1%)	1.22	0.79–1.89
Pregestational diabetes	3 /154 (2.0%)	17/910 (1.9%)	1.09	0.30–3.98
Gestational diabetes	7/154 (4.6%)	86/910 (9.5%)	0.49	0.22–1.09
Male sex	86/153 (56.2%)	454/910 (49.9%)	1.39	0.94–1.92

Note: Missing values due to fewer data stored in the Register of Induced Abortions.

3 | RESULTS

One-hundred-eighty-eight cases of gastroschisis were identified and compared with 910 matched controls. Gastroschisis cases included 148 live births, 5 stillbirths and 35 elective terminations of pregnancy. In univariate analysis, nulliparity was a significant risk factor for gastroschisis, OR 1.65 (95% CI 1.14–2.39). Similarly, smoking appeared to increase the risk for gastroschisis, OR 1.35 (95% CI 0.92–1.99). There were 100 obese mothers (BMI ≥30) in our cohort (9.7%) and obesity was associated with significantly lower risk of gastroschisis, OR 0.39 (95% CI 0.16–0.91). Gestational diabetes also had moderate protective influence, OR 0.49 (95% CI 0.22–1.09). Number of previous miscarriages, and the sex of the newborn/fetus did not affect the risk of gastroschisis. (Table 1) Diabetes groups were the only maternal illnesses included in the analyses as all other groups contained only fewer than five affected mothers in whole cohort.

Maternal age for gastroschisis cases was significantly lower than mean maternal age in the Finnish population (mean 24.3 [*SD* 4.6] years vs 30.0 years, $p < .001$). No significant changes in risk was associated with any prescription drugs used during the first trimester of pregnancy. (Table 2).

Our multivariable analysis provided comparable results with the univariate model: nulliparity, aOR 2.00 (95% CI 1.28–3.11), smoking, aOR: 1.35 (95% CI 0.90–2.03) increased the risk while maternal obesity was protective. Due to significant interaction between maternal BMI and gestational diabetes, these variables were analyzed both separately and together. Protective influence was significantly associated with BMI, aOR 0.30 (95% CI 0.11–0.86). All risk factors included in multivariable analysis are presented in Figure 1.

4 | DISCUSSION

We have demonstrated that nulliparity and young maternal age were significant risk factors for gastroschisis. Maternal obesity, on the other hand, significantly mitigated the risk of gastroschisis.

Consistent with previous reports we found nulliparity to be a significant risk factor (Duong et al., 2012; Rittler, Castilla, Chambers, & Lopez-Camelo, 2007). However, as Rittler et al. compared epidemiologic variables between

TABLE 2 Univariate analysis of all analyzed prescription drugs used in early pregnancy

	Number of events			
	Cases (n = 172)	Controls (n = 838)	Odds ratio	95% CI
Penicillins	20 (11.6%)	104 (12.4%)	0.97	0.58–1.62
Pseudoephedrine	2 (1.2%)	1 (0.1%)	10.0	0.91–110
Nonsteroidal anti-inflammatory drugs	12 (7.0%)	75 (9.0%)	0.72	0.38–1.39
Inhaled steroids	10 (5.8%)	36 (4.3%)	1.44	0.70–2.95
Hormonal drugs for infertility	2 (1.2%)	15 (1.8%)	0.70	0.16–3.19
Antihistamines	8 (4.7%)	24 (2.9%)	1.65	0.70–3.89

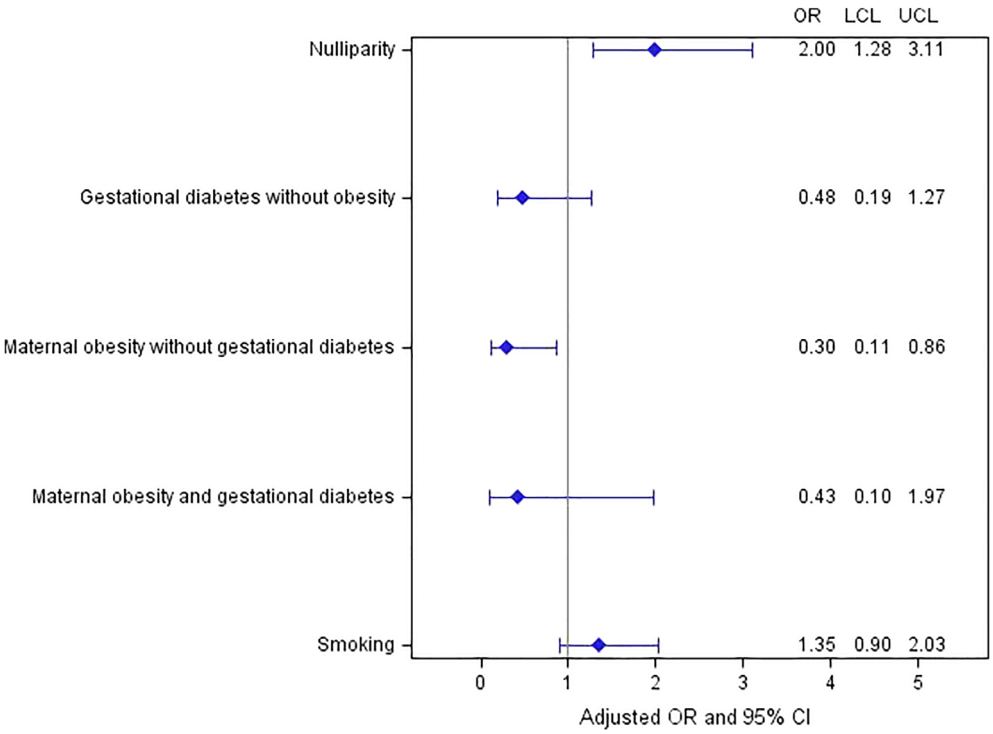

FIGURE 1 Multivariable analysis of the risk factors of gastroschisis. Gestational diabetes and obesity were analyzed both independently and together

primiparae and multiparae, and between those who had and had not changed partners, only length of cohabitation showed significant risk (Rittler et al., 2007). They found no significant risk associated with nulliparity or change of paternity alone. They speculated that some antigenic or immunologic factors could be involved in the origin of gastroschisis.

In our case–control study design we were unable to assess the maternal age as a risk factor, as the controls were age-matched. However, comparing the maternal age of the gastroschisis cases with the average age of mothers during the same time period, revealed a significantly lower age in the mothers of the affected infants, which is in keeping with previous studies (Chabra et al., 2011; Loane et al., 2007; Robledo-Aceves et al., 2015; Vu et al., 2008). Even though the maternal age is the most consistent risk factor of gastroschisis, no explanation for it has been found. It has been speculated that the lifestyle of adolescent mothers would expose them to more risk factors (opioids, smoking, alcohol, illicit drug use). However, recent findings suggest that these exposures alone do not account for the strong inverse association between age and gastroschisis risk (Werler et al., 2018). We speculate, that young mothers possibly have shorter relationships with their partners, as short length of sexual cohabitation is associated with increased risk (Kapapa, Rieg, Henne-Bruns, & Serra, 2020; Rittler et al., 2007). Also, chlamydia infections, a known risk factor for gastroschisis (Dewberry et al., 2020), are more common among young women in Finland (Vuorenmaa, Ilola, & Mussalo-Rauhamaa, 2012). While majority of infections can be asymptomatic (Detels et al., 2011), and chlamydia is not routinely screened at prenatal visits in Finland, it remains as a difficult risk factor to evaluate in our country.

Smoking is one of the most commonly agreed upon risk factors of gastroschisis (Draper et al., 2008; Hackshaw et al., 2011; Hawkins & Baum, 2019) even with cessation in the first trimester (Perry, Mulcahy, & DeFranco, 2019). Placental arteries of smokers have altered mechanical and functional properties, which may compromise the fetal placental blood flow (Clausen, Jorgensen, & Ottesen, 1999). A recent US study found that tobacco tax increases significantly reduced the risk of gastroschisis among other birth defects (Hawkins & Baum, 2019). Hence, smoking prevention programs, including cigarette taxes, could provide a population-level intervention that would help reduce prenatal smoking and the risk of birth defects. In our study, however, smoking was not statistically significant risk factor.

Our study supports the previous findings regarding the elevated risk of gastroschisis associated with the use of pseudoephedrine. Pseudoephedrine is a vasoconstrictive decongestant (Brunton, Hilal-Dandan, & Knollmann, 2017), only available in Finland with a prescription and as a combination drug with antihistamines (desloratadine, acrivastine or cetirizine) (Pharmaca Fennica, 2019). As in earlier reports, we found that pseudoephedrine was modestly associated with gastroschisis risk. Even though our findings were not statistically significant, all reports have been consistent with the elevated risk associated with pseudoephedrine use in

early pregnancy (Torfs, Katz, Bateson, Lam, & Curry, 1996; Werler et al., 2002; Werler, Mitchell, & Shapiro, 1992). As no increased risk was associated with any antihistamines alone, we believe that the elevated risk is associated with the vasoconstrictive characteristics of pseudoephedrine.

Reduced risk of gastroschisis among obese mothers has been established in several studies (Baer et al., 2015; Jenkins et al., 2014; Khodr et al., 2013; Stothard, Tennant, Bell, & Rankin, 2009). It has been speculated this to be due to association between BMI and age, as there is an invert association between maternal age and gastroschisis risk (Stothard et al., 2009). However, we also found maternal obesity to be protective despite having age-matched controls. Hence, maternal obesity appears to be an independent protective factor for gastroschisis regardless of maternal age as reported by Baer et al. (Baer et al., 2015). Previous studies have associated maternal diabetes with both increased (Skarsgard et al., 2015) and decreased (Baer et al., 2015; Given et al., 2017) risk of gastroschisis. According to our results, it appears that protective influence would be associated with obesity rather than diabetes. Regardless, hyperglycemia does not seem to be associated with increased risk.

The strength of our study was the use of validated, high-quality register data with total population coverage (Artama, Gissler, Malm, & Ritvanen, 2011). The main limitations are a relatively small sample size and that this study solely relies on the accuracy of register data. Study is also limited by fewer data collected in the register of induced abortion causing missing values compared to birth register.

In conclusion, nulliparity is associated with increased risk of gastroschisis. Maternal obesity is an independent protective factor for gastroschisis regardless of maternal age and diabetes.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Helenius: Study conception and design; acquisition of data; analysis and interpretation of data. Raitio: Study conception and design; acquisition of data; Analysis and interpretation of data; drafting of manuscript. Hyvärinen: Study conception and design. Tauriainen: Study conception and design; acquisition of data. Leinonen: Acquisition of data; analysis and interpretation of data. Gissler, Syvänen, and Sankilampi: Acquisition of data. Kemppainen and Löyttyniemi: Analysis and interpretation of data. Critical revisions were done by all authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

Ahrens, K. A., Anderka, M. T., Feldkamp, M. L., Canfield, M. A., Mitchell, A. A., Werler, M. M., & National Birth Defects Prevention Study. (2013). Antiherpetic medication use and the risk of gastroschisis: Findings from the National Birth Defects Prevention Study, 1997-2007. *Paediatric and Perinatal Epidemiology*, *27*, 340–345. https://doi.org/10.1111/ppe.12064

Anderson, K. N., Dutton, A. C., Broussard, C. S., Farr, S. L., Lind, J. N., Visser, S. N., ... Tinker, S. C. (2020). ADHD medication use during pregnancy and risk for selected birth defects: National Birth Defects Prevention Study, 1998-2011. *Journal of Attention Disorders*, *24*(3), 479–489. https://doi.org/10.1177/1087054718759753

Artama, M., Gissler, M., Malm, H., & Ritvanen, A. (2011). Nationwide register-based surveillance system on drugs and pregnancy in Finland 1996-2006. *Pharmacoepidemiology and Drug Safety*, *20*, 729–738. https://doi.org/10.1002/pds.2159

Baer, R. J., Chambers, C. D., Jones, K. L., Shew, S. B., MacKenzie, T. C., Shaw, G. M., & Jelliffe-Pawlowski, L. L. (2015). Maternal factors associated with the occurrence of gastroschisis. *American Journal of Medical Genetics.Part A*, *167*, 1534–1541. https://doi.org/10.1002/ajmg.a.37016

Bargy, F., & Beaudoin, S. (2014). Comprehensive developmental mechanisms in gastroschisis. *Fetal Diagnosis and Therapy*, *36*, 223–230. https://doi.org/10.1159/000360080

Beaudoin, S. (2018). Insights into the etiology and embryology of gastroschisis. *Seminars in Pediatric Surgery*, *27*, 283–288. https://doi.org/10.1053/j.sempedsurg.2018.08.005

Bhatt, P., Lekshminarayanan, A., Donda, K., Dapaah-Siakwan, F., Thakkar, B., Parat, S., ... Billimoria, Z. (2018). Trends in incidence and outcomes of gastroschisis in the United States: Analysis of the national inpatient sample 2010-2014. *Pediatric Surgery International*, *34*, 919–929. https://doi.org/10.1007/s00383-018-4308-3

Brunton, L. L., Hilal-Dandan, R., & Knollmann, B. C. (2017). *Goodman & Gilman's: The pharmacological basis of therapeutics* (13th ed.). New York, NY: McGraw-Hill Medical.

Castilla, E. E., Mastroiacovo, P., & Orioli, I. M. (2008). Gastroschisis: International epidemiology and public health perspectives. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *148C*, 162–179. https://doi.org/10.1002/ajmg.c.30181

Chabra, S., Gleason, C. A., Seidel, K., & Williams, M. A. (2011). Rising prevalence of gastroschisis in Washington state. *Journal of*

Toxicology and Environmental Health. Part A, *74*, 336–345. https://doi.org/10.1080/15287394.2011.534424

Clausen, H. V., Jorgensen, J. C., & Ottesen, B. (1999). Stem villous arteries from the placentas of heavy smokers: Functional and mechanical properties. *Obstetrics and Gynecology*, *180*, 476–482. https://doi.org/10.1016/s0002-9378(99)70235-8

Detels, R., Green, A. M., Klausner, J. D., Katzenstein, D., Gaydos, C., Handsfield, H. H., ... Quinn, T. C. (2011). The incidence and correlates of symptomatic and asymptomatic chlamydia trachomatis and *Neisseria gonorrhoeae* infections in selected populations in five countries. *Sexually Transmitted Diseases*, *38*, 503–509.

Dewberry, L. C., Kalia, N., Vazquez, J., Hilton, S. A., Zaretsky, M. V., Behrendt, N., ... Liechty, K. W. (2020). Determining maternal risk factors for gastroschisis using Colorado's birth registry database. *Journal of Pediatric Surgery*, https://doi.org/10.1016/j.jpedsurg.2020.02.030

Draper, E. S., Rankin, J., Tonks, A. M., Abrams, K. R., Field, D. J., Clarke, M., & Kurinczuk, J. J. (2008). Recreational drug use: A major risk factor for gastroschisis?*American Journal of Epidemiology*, *167*, 485–491. https://doi.org/10.1093/aje/kwm335

Duong, H. T., Hoyt, A. T., Carmichael, S. L., Gilboa, S. M., Canfield, M. A., Case, A., ... Waller, D. K. (2012). Is maternal parity an independent risk factor for birth defects?*Birth Defects Research. Part A, Clinical and Molecular Teratology*, *94*, 230–236. https://doi.org/10.1002/bdra.22889

Feldkamp, M. L., & Botto, L. D. (2008). Developing a research and public health agenda for gastroschisis: How do we bridge the gap between what is known and what is not?*American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *148C*, 155–161. https://doi.org/10.1002/ajmg.c.30183

Gissler, M., Teperi, J., Hemminki, E., & Meriläinen, J. (1995). Data quality after restructuring a national medical registry. *Scandinavian Journal of Social Medicine*, *23*, 75–80. https://doi.org/10.1177/140349489502300113

Given, J. E., Loane, M., Garne, E., Nelen, V., Barisic, I., Randrianaivo, H., ... Dolk, H. (2017). Gastroschisis in Europe – A Case-malformed-control study of medication and maternal illness during pregnancy as risk factors. *Paediatric and Perinatal Epidemiology*, *31*, 549–559. https://doi.org/10.1111/ppe.12401

Hackshaw, A., Rodeck, C., & Boniface, S. (2011). Maternal smoking in pregnancy and birth defects: A systematic review based on 173 687 malformed cases and 11.7 million controls. *Human Reproduction Update*, *17*, 589–604. https://doi.org/10.1093/humupd/dmr022

Hawkins, S. S., & Baum, C. F. (2019). Impact of state tobacco control policies on birth defects. *Preventive Medicine*, *127*, 105791. https://doi.org/10.1016/j.ypmed.2019.105791

Jenkins, M. M., Reefhuis, J., Gallagher, M. L., Mulle, J. G., Hoffmann, T. J., Koontz, D. A., ... Honein, M. A. (2014). Maternal smoking, xenobiotic metabolizing enzyme gene variants, and gastroschisis risk. *American Journal of Medical Genetics. Part A*, *164A*, 1454–1463. https://doi.org/10.1002/ajmg.a.36478

Kapapa, M., Rieg, T., Henne-Bruns, D., & Serra, A. (2020). Risk factors for abdominal wall defects. *Congenital Anomalies*, *60*(2), 54–61. https://doi.org/10.1111/cga.12336

Kela. 2019. The Social Insurance Institution of Finland. https://www.kela.fi/tilastojulkaisut_suomen-laaketilasto. Accessed September 25, 2019.

Khodr, Z. G., Lupo, P. J., Canfield, M. A., Chan, W., Cai, Y., & Mitchell, L. E. (2013). Hispanic ethnicity and acculturation, maternal age and the risk of gastroschisis in the national birth defects prevention study. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *97*, 538–545. https://doi.org/10.1002/bdra.23140

Leoncini, E., Botto, L. D., Cocchi, G., Annerén, G., Bower, C., Halliday, J., ... Mastroiacovo, P. (2010). How valid are the rates of down syndrome internationally? Findings from the international clearinghouse for birth defects surveillance and research. *American Journal of Medical Genetics. Part A*, *152A*, 1670–1680. https://doi.org/10.1002/ajmg.a.33493

Loane, M., Dolk, H., Bradbury, I., & EUROCAT Working Group. (2007). Increasing prevalence of gastroschisis in Europe 1980-2002: A phenomenon restricted to younger mothers?*Paediatric and Perinatal Epidemiology*, *21*, 363–369. https://doi.org/10.1111/j.1365-3016.2007.00820.x

Mattix, K. D., Winchester, P. D., & Scherer, L. R. T. (2007). Incidence of abdominal wall defects is related to surface water atrazine and nitrate levels. *Journal of Pediatric Surgery*, *42*, 947–949. https://doi.org/10.1016/j.jpedsurg.2007.01.027

Pakkasjärvi, N., Ritvanen, A., Herva, R., Peltonen, L., Kestilä, M., & Ignatius, J. (2006). Lethal congenital contracture syndrome (LCCS) and other lethal arthrogryposes in Finland—An epidemiological study. *American Journal of Medical Genetics. Part A*, *140A*, 1834–1839. https://doi.org/10.1002/ajmg.a.31381

Opitz, J. M., Feldkamp, M. L., & Botto, L. D. (2019). An evolutionary and developmental biology approach to gastroschisis. *Birth Defects Research*, *111*, 294–311. https://doi.org/10.1002/bdr2.1481

Perry, M. F., Mulcahy, H., & DeFranco, E. A. (2019). Influence of periconception smoking behavior on birth defect risk. *Obstet Gynecol*, *220*, 588.e–588.e7. https://doi.org/10.1016/j.ajog.2019.02.029

Pharmaca Fennica. 2019. Pharmaca Fennica. Accessed October 29, 2019.

Raitio, A., Lahtinen, A., Syvänen, J., Kemppainen, T., Löyttyniemi, E., Gissler, M., ... Helenius, I. (2019). Gastroschisis in Finland 1993 to 2014-increasing prevalence, high rates of abortion, and survival: A population-based study. *European Journal of Pediatric Surgery*, https://doi.org/10.1055/s-0039-3401797

Rittler, M., Castilla, E. E., Chambers, C., & Lopez-Camelo, J. S. (2007). Risk for gastroschisis in primigravidity, length of sexual cohabitation, and change in paternity. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *79*, 483–487. https://doi.org/10.1002/bdra.20364

Rittler, M., Vauthay, L., & Mazzitelli, N. (2013). Gastroschisis is a defect of the umbilical ring: Evidence from morphological evaluation of stillborn fetuses. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *97*, 198–209. https://doi.org/10.1002/bdra.23130

Robledo-Aceves, M., Bobadilla-Morales, L., Mellin-Sanchez, E. L., Corona-Rivera, A., Perez-Molina, J. J., Cardenas-Ruiz Velasco, J. J., & Corona-Rivera, J. R. (2015). Prevalence and risk factors for gastroschisis in a public hospital from West Mexico. *Congenital Anomalies*, *55*, 73–80. https://doi.org/10.1111/cga.12087

Short, T. D., Stallings, E. B., Isenburg, J., O'Leary, L. A., Yazdy, M. M., Bohm, M. K., ... Reefhuis, J. (2019). Gastroschisis trends and ecologic link to opioid prescription rates - United States, 2006-2015. *Morbidity and Mortality Weekly Report*, *68*, 31–36. https://doi.org/10.15585/mmwr.mm6802a2

Skarsgard, E. D., Meaney, C., Bassil, K., Brindle, M., Arbour, L., & Moineddin, R. (2015). Maternal risk factors for gastroschisis in Canada. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *103*, 111–118. https://doi.org/10.1002/bdra.23349

Souther, C., Puapong, D. P., Woo, R., & Johnson, S. M. (2017). Possible etiologies of increased incidence of gastroschisis. *Pediatric Surgery International*, *33*, 1209–1213. https://doi.org/10.1007/s00383-017-4166-4

Stothard, K. J., Tennant, P. W. G., Bell, R., & Rankin, J. (2009). Maternal overweight and obesity and the risk of congenital anomalies: A systematic review and meta-analysis. *JAMA*, *301*, 636–650. https://doi.org/10.1001/jama.2009.113

Torfs, C. P., Katz, E. A., Bateson, T. F., Lam, P. K., & Curry, C. J. (1996). Maternal medications and environmental exposures as risk factors for gastroschisis. *Teratology*, *54*, 84–92. https://doi.org/10.1002/(SICI)1096-9926(199606)54:2<84::AID-TERA4>3.0.CO;2-4

Vu, L. T., Nobuhara, K. K., Laurent, C., & Shaw, G. M. (2008). Increasing prevalence of gastroschisis: Population-based study in California. *The Journal of Pediatrics*, *152*, 807–811. https://doi.org/10.1016/j.jpeds.2007.11.037

VuorenmaaL, IlolaA, Mussalo-RauhamaaH. 2012. Sukupuolitaudit Suomessa – eilen, tänään ja huomenna. Regional State Administrative Agency for Southern Finland. https://www.avi.fi/documents/10191/149165/Sukupuolitaudit+Suomessa+eilen+tanaan+ja+huomenna/6d4060db-df05-4372-a4fc-6633b796fdb2.

Waller, S. A., Paul, K., Peterson, S. E., & Hitti, J. E. (2010). Agricultural-related chemical exposures, season of conception, and risk of gastroschisis in Washington state. *American Journal of Obstetrics and Gynecology*, *202*, 241.e-6. https://doi.org/10.1016/j.ajog.2010.01.023

Werler, M. M., Mitchell, A. A., & Shapiro, S. (1992). First trimester maternal medication use in relation to gastroschisis. *Teratology*, *45*, 361–367. https://doi.org/10.1002/tera.1420450407

Werler, M. M., Guéry, E., Waller, D. K., & Parker, S. E. (2018). Gastroschisis and cumulative stressor exposures. *Epidemiology*, *29*, 721–728. https://doi.org/10.1097/EDE.0000000000000860

Werler, M. M., Sheehan, J. E., & Mitchell, A. A. (2002). Maternal medication use and risks of gastroschisis and small intestinal atresia. *American Journal of Epidemiology*, *155*, 26–31. https://doi.org/10.1093/aje/155.1.26

Winchester, P. D., Huskins, J., & Ying, J. (2009). Agrichemicals in surface water and birth defects in the United States. *Acta Paediatrica*, *98*, 664–669. https://doi.org/10.1111/j.1651-2227.2008.01207.x

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