Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Duodenal atresia: Maternal Risk Factors in Finnish Nationwide Population-based Study from 2004-2017

Suvi Alikärri

stmali@utu.fi

University of Turku and Turku University Hospital

Ilkka Helenius

University of Helsinki and Helsinki University Hospital

Maarit K Leinonen

Finnish Institute for Health and Welfare

Johanna Syvänen

University of Turku and Turku University Hospital

Teemu Kemppainen

University of Turku and Turku University Hospital

Eliisa Löyttyniemi

University of Turku and Turku University Hospital

Mika Gissler

Finnish Institute for Health and Welfare

Arimatias Raitio

University of Turku and Turku University Hospital

Research Article

Keywords: Duodenal atresia, maternal risk factors, congenital anomaly, primiparity

Posted Date: November 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11468420/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Purpose

Duodenal atresia (DA) is known to be strongly linked with trisomy 21 and to cardiac anomalies. However, risk factors for non-genetic DA remain largely unknown. Hence, we set out to identify maternal risk factors for this anomaly.

Methods

All DA cases (n = 249) in 2004–2017 were identified in the Finnish Register of Congenital Malformations. After exclusion of the genetic cases (n = 83), five matched controls for each DA case (n = 166 and n = 830) were randomly selected. Analyzed maternal risk factors were maternal chronic diseases, prescription drugs dispensed during the first trimester of pregnancy, smoking, BMI, and reproductive history.

Results

In multivariable analysis, only primiparity was observed as an independent risk factor (adjusted OR 1.63, 95% CI 1.13–2.35). Antihistamines (ATC-code R06AX) emerged with a potential but inconclusive signal (aOR 3.50, 95% CI 0.91–13.5). Maternal pregestational diabetes (OR 1.68, 95% CI 0.60–4.71), smoking (OR 1.36, 95% CI 0.83–2.22) or BMI (OR 0.55, 95% CI 0.16–1.85 for underweight; OR 0.84, 95% CI 0.57–1.24 for overweight) were not associated with DA.

Conclusions

In our data, only primiparity was associated with non-genetic DA. This and sparsity of previous studies for non-genetic DA highlights the need for future research with higher case numbers.

Introduction

Duodenal atresia and obstruction (DA) is the most common atresia of small bowel with total birth prevalence previously calculated to be in Finland 2.95/10 000[1] and varying from 0.3 to 1.6/10 000 in Europe [1, 2]. The anomaly can be divided into three types: the most common is type 1- mucosal web (67–69%), followed by type 3 - complete separation (6–18%) and type 2 - fibrous cord (2–17%). Additionally duodenal stenosis is noted to be present in 23–33% of cases [3, 4]. According to current knowledge, DA occurs due to a failure of recanalization of the primitive duodenum, whereas jejuno-ileal atresias are more likely happen due to vascular compromises [5–7].

Approximately one fourth to one third of all DA cases have chromosomal abnormalities, mainly trisomy 21 [1, 2, 8, 9]. Cardiac anomalies are the most common associated structural anomaly group presenting in about 30% of all cases [1, 8] and 12% in non-syndromic cases [2]. Common associated anomalies also include other gastrointestinal, limb and urinary tract deformities [1, 2]. Mortality in DA is generally low and driven by severe cardiac anomalies[1].

Risk factors for DA are not clear, and publications of the subject are few in volume. Of maternal characteristics, maternal age [10], parity [11], chronic and acute diseases and infections [12–14] have been postulated to be factors possibly increasing the risk for congenital anomalies, also DA. On the other hand, fish consumption has been noted as possible preventive factor for DA and other gastrointestinal tract anomalies [15]. Regarding medications consumed during pregnancy, recent Swedish study by Heinonen et al. [16] reported 68% of pregnant women used at least one prescription drug during pregnancy. The consumption of medicines to treat nausea, diabetes, high blood pressure and mental conditions had increased during the 15 years investigated [16].

In general, the risk factors for DA are not well studied and also the consumption of different medications has increased in recent years. Against this background, this study aimed to examine maternal risk factors non-genetic DA.

Methods

This is a retrospective, nationwide population-based case-control study and registers used are maintained by the Finnish Institute for Health and Welfare (THL): the Finnish Register of Congenital Malformations (FRM), the Medical Birth Register and the Register of Induced Abortions. Data on congenital anomalies are retrieved from multiple sources. All major cases are confirmed and double checked by a medical geneticist before they are entered to the FRM database. Additional information (patient records, specialist consultations etc.) is added as needed.

Data on maternal reimbursed prescription medicine purchases and chronic illnesses were received from the Register of Reimbursed Drug Purchases and the Register of Entitlements to Reimbursement for Medicine Expenses, maintained by the Social Insurance Institution of Finland (Kela). Reimbursement codes for expenses of medicines purchases (Kela codes) were used to identify potential underlying maternal chronic illnesses.

Several international and national sources have validated these registers of which have nearly 100% accuracy and coverage[17–19]. Finnish Social and Health Data Permit Authority (Findata) has a strict control over all the national register studies. The data collected is stored and analyzed in a trusted research environment (Kapseli®) provided by Findata.

Before conducting this study, the approval of the institutional review board at the University of Turku was received, as well as permission from Findata for data usage was obtained (THL/6258/14.02.00/2020).

Selection of Cases and Controls

During the study period, from January 1st 2004 to December 31st 2017, 249 DA cases were identified. Of these 100 cases (40%) were isolated, 83 were syndromic (33%) and 66 (27%) had other associated anomalies. Of syndromic genetic cases 63 (25%) were trisomy 21. After excluding the genetic cases, we got 166 DA cases with 830 healthy controls for analysis. The genetic cases were excluded from further analysis for minimizing the possibility that genetic/chromosomal DA's in this study would have been incorrectly attributed to medicine leading to an overestimation of potential teratogenic effects. This follows the principles set by the European Surveillance of Congenital Anomalies (EUROCAT, guide 1.5) [19, 20]. For each one DA case, five newborn controls with no other gastrointestinal tract anomaly and their mothers were selected randomly. Controls were matched by the year of birth, maternal age (+/- one year) and geographical area.

The diagnoses in the registers have been coded according to the World Health Organization's International Classification of Diseases, 9th and 10th revisions (ICD-9, Atlanta modification, and ICD-10). The cases with ICD-10 codes Q40.9, Q41, Q41.9, Q43.8 and Q45, and/or with ICD-9 codes 751100 and 751560 were included in the study. The diagnosis was ascertained by the written diagnosis, and in case of discrepancy, case was excluded.

Risk Factors analyzed

Maternal risk factors screened were gestational diabetes mellitus (GDM) (ICD-10 codes O24.4 and O24.9 and/or abnormal glucose tolerance test result), pregestational diabetes mellitus type one and two (E10, E11, O24.0, O24.1, O24.2, O24.3, and Kela codes 103 and 215). Other chronic diseases were defined according to Kela codes. In addition, reproductive history, pre-pregnancy body mass index (BMI), and smoking were analyzed.

Prescription drugs dispensed one month before last menstrual period until the end of first trimester were detected. Data on prescription medicine purchases were collected as ATC-codes (The Anatomical Therapeutic Chemical classification system)[21]. The analyses were performed in the fourth level of ATC-codes, with exception of insulins (ATC-group A10A, third level). A medication group was selected for analysis only if at least 5 mothers of DA child or controls had medication purchase from the group between one month before the last menstrual period and before the end of first trimester. The first trimester of pregnancy is defined as time from the beginning of last menstrual period + 97 days.

In Finland, the first visit to prenatal maternal care clinic is approximately during 8th to 10th week of pregnancy. At this visit, maternal height and weight are systematically recorded from all women. Maternity care clinics and child welfare clinics in Finland reach nearly 100% of all families from all backgrounds, from all socioeconomic groups, also including immigrants[22, 23].

Statistical analysis

All statistical tests were two-sided significance set at $p < 0.05$. The analyses were performed using the SAS System, Windows version 9.4 (SAS Institute Inc., Cary, North Carolina, United States).

The hypothesized risk factors were first evaluated with the Fisher exact test. After that, modelling with univariate logistic regression analysis for case-control studies was started. Factors that were not significant in univariate analysis were not brought to multivariable models. Odds ratios (OR) with 95% confidence intervals (CIs) were reported with the results.

Results

In univariate analysis only primiparity was significant (OR 1.64, 95% CI 1.14–2.37), yet antihistamine group (ATC-group R06AX) had a borderline association with DA (3.61, 0.96–13.64). No association was found with under (0.55, 0.16–1.85) or overweight (0.84, 0.57–1.24), smoking (1.36, 0.83–2.22), pregestational (1.68, 0.60–4.71) or gestational diabetes (0.97, 0.56–1.69). The results of univariate analysis are presented in Table 1.

Multivariable analyses were done for parity and antihistamines, and only primiparity was noted to have an association (aOR 1.63, 1.13–2.35). Antihistamines emerged with a non-significant association (3.50, 0.91–13.5).

ATC-group R06AX contains multiple products. Products that were purchased by our study cohort are presented in Table 2. Due to small number of cases, we were not able to analyze them in more detail.

Table 1
Univariate analysis of maternal risk factors in DA.

Maternal risk factor (ATC-code if convenient)		Cases (N = 166) n (%)	Controls (N = 830) n (%)	Odds Ratio	95% Confidence interwall
Parity	Primiparity	80 (50.3)	331 (39.9)	1.64	1.14–2.37
	Multiparity	79 (49.7)	498 (60.0)	0.61	0.42–0.88
Pregestational diabetes		5 (3.1)	15 (1.8)	1.68	0.60–4.71
Gestational diabetes		17 (10.7)	93(11.2)	0.97	0.56–1.69
Antihistamines (R06AX)		4 (2.4)	6 (0.7)	3.61	0.96–13.64
Smoking	yes	25 (15.1)	107 (46.5)	1.36	0.83–2.22
Body mass index	< 18	3 (1.8)	28 (3.4)	0.55	0.16–1.85
	18-24.99	100 (60.2)	504 (60.8)	reference	reference
	≥ 25	44 (26.5)	266 (32.0)	0.84	0.57–1.24

Table 2
Recorded purchases from the ATC-group R06AX by the study cohort.

ATC-code	Product
Other antihistamines for systemic use - R06AX	
	loratadine
	acrivastine
	fexofenadine
	desloratadine
	bilastine
	ebastine

Discussion

Herein, we observed primiparity to be associated with non-syndromic DA. The tendency towards an association with antihistamines was also noted. No other identified potential risk factors emerged in the analysis, which involved 166 isolated duodenal atresia cases with their age-matched mothers and controls.

Duodenum develops from the distal part of the foregut, simultaneously with pancreas and extrahepatic biliary system and with rotation the bowel. This is guided by the Hedgehog-gene family [4, 24]. During the development, the foregut first grows into a solid cord, as epithelial lining grows faster than the length of the foregut. Then, before the end of first trimester, this solid cord begins to develop a lumen. Error in this vacuolation may result in DA, with or without an annular pancreas [4]. Other extrinsic theories of DA exist, and in those, the continuation of the bowel is complicated by an external compression. These are for example malrotation, pre-portal duodenal vein, superior mesenteric artery-syndrome, duplication cyst of duodenum, as well as sometimes isolated pancreas annulare [4, 6]. This epidemiology of DA differs distinctly from the other small intestinal atresias, which naturally entails a different risk factor profile [7].

Primiparity as a risk factor for congenital anomalies is not a novel finding [25, 26]. Younger age, the size of the uterus and non-healthy life habits have been postulated to be partly behind this [11]. Also, the younger maternal age have been linked to non-chromosomal anomalies, whereas older age-related risk for chromosomal anomalies [27]. In our study, the investigated life habits such as smoking or BMI were not associated with DA. Also, due to age-matching, the correlation between age and DA could not be studied.

In univariate and multivariable analysis, there was a borderline signal with DA and ATC-group R06AX containing loratadine among other antihistamine products (Table 2). Nevertheless, study by Hansen et al.[28] found an association with DA and loratadine or desloratadine (aOR 2.08, 95% CI 1.14–3.80). Generally, antihistamines are regarded safe during pregnancy and are commonly used for nausea and symptoms caused by allergy. [29, 30] Many of them, including loratadine, are sold as over-the-counter (OTC) drugs without prescription. This most likely increases the use of medication, for example in Sweden, where antihistamines (ATC-group R03) were used by 8–10% of women on the first trimester of pregnancy[16, 31]. Due to easy availability, there has been a discussion about association with antihistamines and congenital anomalies, especially loratadine and hypospadias, but this hypothesis has been later overruled by Diav-Citrin et al.[32], Källén et al.[33] and Hansen et al.[28].

Howley et al.[13] analyzed urinary tract infections (UTI) during the first trimester to associate with DA, as well as with small intestinal atresias. In our study, we found no association with drugs used to treat UTI and DA. A recent study of Tahkola et al.[7] demonstrated an association with non-steroidal anti-inflammatory drugs (NSAIDs) and jejuno-ileal atresias. Neither did we find an association with NSAIDs in this study. This is logic as etiologies of these anomalies differ: jejuno-ileal atresias are more likely to happen due to vascular reasons [2]. In rodent models, doxorubicin, an anthracycline group chemotherapeutical agent, was noted to increase the prevalence of DA, as well as EA [14]. Later this association with doxorubicine and DA was not detected in the studies of Germann et al.[34] and not in

EUROmediCAT-study neither [35]. In our study, no malignant diseases potentially graving chemotherapy emerged. However, we had no information about medicines administrated in hospitals and all patients with malignant diseases may not have specific reimbursement code for their disease.

Generally, maternal risk factors for other structural congenital anomalies are studied more while studies for non-genetic DA's risk factors are scarcer. Oxidative stress during the very beginning of the development due to hyperglycemia is identified as a risk factor for congenital anomalies [12, 36]. Use of contraceptive pill during conception and early pregnancy have been observed a potential risk factor, having association to cleft palate and gastroschisis [37]. In addition, congenital vertebral anomalies and estrogens used in assisted reproductive technologies seemed to have an association [38]. In our yet not published results concerning esophageal atresia's risk factors, we found an association between EA and some estrogen products mainly used as contraceptives and locally (ATC-group G03CA). In this current study, there was no signal between DA and any estrogen product. However, contraceptives are reimbursed in Finland only when they are used to treat medical condition such as endometriosis. Local estrogen products are not reimbursed either and are available OTC, which might cause a bias in the results.

According to our previous study, ca. 40% of the DA cases are isolated, 25% of all DA cases are presented with chromosomal abnormalities, mainly Trisomy 21, and 27% with other major congenital anomaly, most importantly cardiac anomalies, which were present in 36% [1]. Pijpers et. al. [8] had similar results as they analyzed cardiac anomalies to be present in 31% of the cases, and further, cardiac anomalies to be associated with trisomy 21. Later, in meta-analysis, they came to a conclusion that increased occurrence of cardiac anomalies in DA patients is related to DA itself, not only to Trisomy 21 as the proportions of cardiac anomalies in patient groups were almost equal, 15 and 16% (DA + trisomy 21 + no cardiac anomaly and DA + trisomy 21 + cardiac anomaly, respectively) [39]. For trisomy 21, maternal use of contraceptive pills at peri-conception time simultaneously with smoking has been postulated as exposure agents altering the meiosis, as well as maternal advanced age and weight [40]. In persons with trisomy 21, DA is noted to be present in 3% of cases [41].

Strengths and limitations

This study is among the largest retrospective, case-control studies of non-genetic DA's risk factors, and we only found primiparity to have an association. In the study, we were able to analyze the role of maternal illnesses and consumption of prescription drugs from one month prior the last menstrual period to the end of the first trimester to DA. This was possible because of the high-quality and nearly 100% population coverage registers mentioned earlier [17–19]. The greatest limitation of this study is the low number of cases due to rarity of the studied anomaly. Also, this study does not contain the information of OTC-drugs which might result in misclassification bias as many products, for example some antihistamines and pain killers, are quite freely available [42].

Conclusions

In this retrospective case-control study we were able to demonstrate that primiparity is associated with non-genetic duodenal atresia. As no other factor emerged, this information may be relieving for families. Regardless, sparsity of studies about maternal risk factors for non-genetic DA highlights the need for future research with higher case numbers.

Declarations

Funding

and Competing interests

Suvi Alikärri: Päivikki & Sakari Sohlberg Foundation, Scientific funding to Institution from Finnish State Funding via Helsinki and Turku University Hospitals and from the Finnish Pediatric Research Foundation.

Ilkka Helenius: Scientific funding to Institution from Finnish State Funding via Helsinki and Turku University Hospitals, Finnish Paediatric Research Foundation, Päivikki and Sakari Sohlberg Foundation, Liv och Hälsa. Consultant for Medtronic.

Maarit K Leinonen: No funding

Johanna Syvänen: No funding

Teemu Kemppainen: No funding

Eliisa Löyttyniemi: No funding

Mika Gissler: No funding

Arimatias Raitio: Scientific funding to Institution from the Finnish Pediatric Research Foundation, Päivikkki ja Sakari Sohlberg Foundation via Turku University Hospital.

Author Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Eliisa Löyttyniemi, Teemu Kemppainen and Suvi Alikärri. The first draft of the manuscript was written by Suvi Alikärri and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

References

1. Alikarri S, Helenius I, Heiskanen S et al. Duodenal Atresia in Finland from 2004 to 2017: Prevalence, Mortality, and Associated Anomalies-A Population-Based Study. Eur J Pediatr Surg 2024; 34: 544–549. DOI: 10.1055/a-2338-5873

2. Best KE, Tennant PW, Addor MC et al. Epidemiology of small intestinal atresia in Europe: a register-based study. Arch Dis Child Fetal Neonatal Ed 2012; 97: F353–358. DOI: 10.1136/fetalneonatal-2011-300631

3. Dalla Vecchia LK, Grosfeld JL, West KW et al. Intestinal atresia and stenosis: a 25-year experience with 277 cases. Arch Surg 1998; 133: 490–496; discussion 496–497. DOI: 10.1001/archsurg.133.5.490

4. Grosfeld JL, Rescorla FJ. Duodenal atresia and stenosis: reassessment of treatment and outcome based on antenatal diagnosis, pathologic variance, and long-term follow-up. World J Surg 1993; 17: 301–309. DOI: 10.1007/BF01658696

5. Miscia ME, Lauriti G, Lelli Chiesa P et al. Duodenal atresia and associated intestinal atresia: a cohort study and review of the literature. Pediatr Surg Int 2019; 35: 151–157. DOI: 10.1007/s00383-018-4387-1

6. Brinkley MF, Tracy ET, Maxfield CM. Congenital duodenal obstruction: causes and imaging approach. Pediatr Radiol 2016; 46: 1084–1095. DOI: 10.1007/s00247-016-3603-1

7. Tahkola E, Raitio A, Helenius I et al. Intestinal Atresia in Finland: Maternal Risk Factors, Prevalence, Associated Anomalies and Survival. Acta Paediatr 2026. DOI: 10.1111/apa.70450

8. Pijpers AGH, Eeftinck Schattenkerk LD, Straver B et al. The Incidence of Associated Anomalies in Children with Congenital Duodenal Obstruction-A Retrospective Cohort Study of 112 Patients. Children (Basel) 2022; 9. DOI: 10.3390/children9121814

9. Choudhry MS, Rahman N, Boyd P et al. Duodenal atresia: associated anomalies, prenatal diagnosis and outcome. Pediatr Surg Int 2009; 25: 727–730. DOI: 10.1007/s00383-009-2406-y

10. Kyyrönen P, Hemminki K. Gastro-intestinal atresias in Finland in 1970-79, indicating time-place clustering. J Epidemiol Community Health 1988; 42: 257–265. DOI: 10.1136/jech.42.3.257

11. Duong HT, Hoyt AT, Carmichael SL et al. Is maternal parity an independent risk factor for birth defects? Birth Defects Res A Clin Mol Teratol 2012; 94: 230–236. DOI: 10.1002/bdra.22889

12. Kinnunen J, Nikkinen H, Keikkala E et al. Gestational diabetes is associated with the risk of offspring's congenital anomalies: a register-based cohort study. BMC Pregnancy Childbirth 2023; 23: 708. DOI: 10.1186/s12884-023-05996-6

13. Howley MM, Feldkamp ML, Papadopoulos EA et al. Maternal genitourinary infections and risk of birth defects in the National Birth Defects Prevention Study. Birth Defects Res 2018; 110: 1443–1454. DOI: 10.1002/bdr2.1409

14. Diez-Pardo JA, Baoquan Q, Navarro C et al. A new rodent experimental model of esophageal atresia and tracheoesophageal fistula: preliminary report. J Pediatr Surg 1996; 31: 498–502. DOI: 10.1016/s0022-3468(96)90482-0

15. Michikawa T, Yamazaki S, Ono M et al. Fish consumption in early pregnancy and congenital gastrointestinal tract atresia in the Japan Environment and Children's Study. Br J Nutr 2019; 121: 100–108. DOI: 10.1017/S0007114518002842

16. Heinonen EW, Smew AI, Chacon SS et al. Prescription Medication Use During Pregnancy and Postpartum in Sweden 2007 to 2022. Pharmacoepidemiol Drug Saf 2026; 35: e70473. DOI: 10.1002/pds.70473

17. Gissler M, Teperi J, Hemminki E et al. Data quality after restructuring a national medical registry. Scand J Soc Med 1995; 23: 75–80. DOI: 10.1177/140349489502300113

18. THL. National Institute of Health and Welfare. The Finnish Register of Congenital Malformations. Available at

https://thl.fi/en/data-and-statistics/data-quality/quality-reports-on-statistics/quality-report-congenital-malformations. In:

19. 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. DOI: 10.1002/bdra.20775

20. EUROCAT. European surveillance of congenital anomalies. Available at www.eurocat-network.eu. In:

21. Organisation WH. WHO Collaborating Centre for Drug Statistics Methodology. In:

22. Riikka Riihonen TH, Suvi Luomala. ”Terveiden lasten tarkastamista” – mitä hyötyä neuvolapalveluista on? Lääketieteellinen Aikakauskirja Duodecim 2021; 2021;137(23):2567-72.

23. Maaret Vuorenmaa RK, Vesa Saaristo, Kirsi Wiss. Enemmistö vauvaperheiden vanhemmista on tyytyväisiä neuvolapalveluihin – perheen hyvinvoinnin selvittämisessä ja vanhemmuuden tukemisessa

parannettavaa. In: The Finnish Institute of Health and Welfare (THL); 2023:

24. van den Brink GR. Hedgehog signaling in development and homeostasis of the gastrointestinal tract. Physiol Rev 2007; 87: 1343–1375. DOI: 10.1152/physrev.00054.2006

25. Syvanen J, Raitio A, Nietosvaara Y et al. Risk Factors and Prevalence of Limb Deficiencies Associated With Amniotic Band Sequence: A Population-based Case-control Study. J Pediatr Orthop 2021; 41: e94–e97. DOI: 10.1097/BPO.0000000000001686

26. Syvanen J, Nietosvaara Y, Hurme S et al. Maternal risk factors for congenital limb deficiencies: A population-based case-control study. Paediatr Perinat Epidemiol 2021; 35: 450–458. DOI: 10.1111/ppe.12740

27. Loane M, Dolk H, Morris JK et al. Maternal age-specific risk of non-chromosomal anomalies. BJOG 2009; 116: 1111–1119. DOI: 10.1111/j.1471-0528.2009.02227.x

28. Hansen C, Desrosiers TA, Wisniewski K et al. Use of antihistamine medications during early pregnancy and selected birth defects: The National Birth Defects Prevention Study, 1997–2011. Birth Defects Res 2020; 112: 1234–1252. DOI: 10.1002/bdr2.1749

29. Gilboa SM, Strickland MJ, Olshan AF et al. Use of antihistamine medications during early pregnancy and isolated major malformations. Birth Defects Res A Clin Mol Teratol 2009; 85: 137–150. DOI: 10.1002/bdra.20513

30. Kallen B. Use of antihistamine drugs in early pregnancy and delivery outcome. J Matern Fetal Neonatal Med 2002; 11: 146–152. DOI: 10.1080/jmf.11.3.146.152

31. Stephansson O, Granath F, Svensson T et al. Drug use during pregnancy in Sweden - assessed by the Prescribed Drug Register and the Medical Birth Register. Clin Epidemiol 2011; 3: 43–50. DOI: 10.2147/CLEP.S16305

32. Diav-Citrin O, Shechtman S, Aharonovich A et al. Pregnancy outcome after gestational exposure to loratadine or antihistamines: a prospective controlled cohort study. J Allergy Clin Immunol 2003; 111: 1239–1243. DOI: 10.1067/mai.2003.1499

33. Kallen B, Olausson PO. No increased risk of infant hypospadias after maternal use of loratadine in early pregnancy. Int J Med Sci 2006; 3: 106–107. DOI: 10.7150/ijms.3.106

34. Germann N, Goffinet F, Goldwasser F. Anthracyclines during pregnancy: embryo-fetal outcome in 160 patients. Ann Oncol 2004; 15: 146–150. DOI: 10.1093/annonc/mdh009

35. Given JE, Loane M, Luteijn JM et al. EUROmediCAT signal detection: an evaluation of selected congenital anomaly-medication associations. Br J Clin Pharmacol 2016; 82: 1094–1109. DOI: 10.1111/bcp.12947

36. Eriksson UJ, Borg LA, Cederberg J et al. Pathogenesis of diabetes-induced congenital malformations. Ups J Med Sci 2000; 105: 53–84. DOI: 10.1517/03009734000000055

37. Waller DK, Gallaway MS, Taylor LG et al. Use of oral contraceptives in pregnancy and major structural birth defects in offspring. Epidemiology 2010; 21: 232–239. DOI: 10.1097/EDE.0b013e3181c9fbb3

38. Raitio A, Heiskanen S, Syvanen J et al. Maternal Risk Factors for Congenital Vertebral Anomalies: A Population-Based Study. J Bone Joint Surg Am 2023; 105: 1087–1092. DOI: 10.2106/JBJS.22.01370

39. Pijpers AGH, Eeftinck Schattenkerk LD, de Vries R et al. Cardiac anomalies in children with congenital duodenal obstruction: a systematic review with meta-analysis. Pediatr Surg Int 2023; 39: 160. DOI: 10.1007/s00383-023-05449-3

40. Coppede F. Risk factors for Down syndrome. Arch Toxicol 2016; 90: 2917–2929. DOI: 10.1007/s00204-016-1843-3

41. Atiyat DK, Al-Nusair DA, Alhajahjeh A et al. Global Prevalence of Duodenal Atresia in Trisomy 21: A Systematic Review and Meta-Analysis. Eur J Pediatr Surg 2025; 35: 208–218. DOI: 10.1055/a-2471-6435

42. Acton EK, Willis AW, Hennessy S. Core concepts in pharmacoepidemiology: Key biases arising in pharmacoepidemiologic studies. Pharmacoepidemiol Drug Saf 2023; 32: 9–18. DOI: 10.1002/pds.5547