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Maternal Risk Factors for Congenital Vertebral Anomalies

A Population-Based Study

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Background: The spectrum of congenital vertebral defects varies from benign lesions to severe, life-threatening conditions. The etiology and maternal risk factors remain mainly unclear in isolated cases. Hence, we aimed to assess and identify potential maternal risk factors for these anomalies. Based on previous studies, we hypothesized that maternal diabetes, smoking, advanced maternal age, obesity, chronic diseases, and medication used during the first trimester of pregnancy might increase the risk of congenital vertebral malformations.

Methods: We performed a nationwide register-based case-control study. All cases with vertebral anomalies (including live births, stillbirths, and terminations for fetal anomaly) were identified in the Finnish Register of Congenital Malformations from 1997 to 2016. Five matched controls from the same geographic region were randomly selected for each case. Analyzed maternal risk factors included age, body mass index (BMI), parity, smoking, history of miscarriages, chronic diseases, and prescription drugs dispensed during the first trimester of pregnancy.

Results: In total, 256 cases with diagnosed congenital vertebral anomalies were identified. After excluding 66 malformations associated with known syndromes, 190 nonsyndromic malformation cases were included. These were compared with 950 matched controls. Maternal pregestational diabetes was a significant risk factor for congenital vertebral anomalies (adjusted odds ratio [OR], 7.30 [95% confidence interval (CI), 2.53 to 21.09). Also, rheumatoid arthritis (adjusted OR, 22.91 [95% CI, 2.67 to 196.40]), estrogens (adjusted OR, 5.30 [95% CI, 1.57 to 17.8]), and heparins (adjusted OR, 8.94 [95% CI, 1.38 to 57.9]) were associated with elevated risk. In a sensitivity analysis using imputation, maternal smoking was also significantly associated with an elevated risk (adjusted OR, 1.57 [95% CI, 1.05 to 2.34]).

Conclusions: Maternal pregestational diabetes and rheumatoid arthritis increased the risk of congenital vertebral anomalies. Also, estrogens and heparins, both of which are frequently used in assisted reproductive technologies, were associated with an increased risk. Sensitivity analysis suggested an increased risk of vertebral anomalies with maternal smoking, warranting further studies.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Congenital vertebral malformations are typically classified as defects of formation (hemivertebra), defects of segmentation (unilateral bar), and a mixed group[1]. Congenital spinal deformities vary from those that require only observation after identification to challenging spinal deformities including scoliosis or kyphosis, with or without fused ribs, resulting in potentially life-threatening pulmonary insufficiency[2] and spinal cord deficits[3]. Fully segmented hemivertebrae represent the most common indication for a surgical procedure in patients with congenital scoliosis, often necessitating hemivertebrectomy at an early age[4], whereas segmentation defects require an early anteroposterior spinal fusion, distraction-based spinal instrumentation, or thoracostomy and chest distraction[2].

The vertebrae develop from mesenchymal cells during the third to eighth gestational weeks. Disturbance during this process of somatogenesis leads to vertebral malformations. It has been estimated that the prevalence of congenital vertebral malformations is approximately 5 to 10 per 10,000 births, although the true incidence is unknown because asymptomatic individuals do not seek medical care[5]. A recent population-based study showed a

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total prevalence of 2.2 per 10,000 births, with a significantly increasing trend[6]. This increasing trend calls for more detailed evaluation of the risk factors for congenital spinal deformities.

Malformations may be an isolated finding, may be associated with other malformations, or may be part of an underlying chromosomal abnormality or syndrome. With a lack of evidence to suggest otherwise, the prevailing assumption is that most cases encountered are clinically sporadic (i.e., not familial). According to previous studies, 18% to 39% of all cases are isolated vertebral anomalies[6,7]. A small group of cases, between 5% and 10%, have a genetic background involving different syndromes, such as Klippel-Feil or VACTERL (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal and radial abnormalities, and limb abnormalities)[8,9].

It has been postulated that a combination of genetic predisposition with environmental factors represents the most common etiology of congenital vertebral malformations[10]. In a multicenter, retrospective, case-control study, maternal risk factors during the pregnancy were identified in approximately 20% of cases of congenital vertebral malformation[11]. Previously reported risk factors for congenital vertebral malformation include hyperthermia[5], anticonvulsant medication[11,12], maternal alcohol use[5], maternal insulin-dependent diabetes mellitus[13], and gestational diabetes[13,14]. Anoxia created by carbon monoxide exposure at a critical time in mouse and chick models has been demonstrated to cause congenital vertebral malformations very similar to those in humans, and in a dose-dependent fashion[15,16]. However, there has been limited knowledge regarding the contribution of environmental factors to the occurrence of congenital vertebral malformations.

The aim of our study was to identify potential maternal risk factors for congenital vertebral anomalies. We hypothesized that maternal diabetes, smoking, advanced maternal age, obesity, chronic diseases, primiparity, and medication used during the first trimester of pregnancy might increase the risk of these anomalies.

Materials and Methods

The study is based on the data from the Finnish Register of Congenital Malformations (FRM), the Medical Birth Register, and the Register of Induced Abortions, which are all maintained by the Finnish Institute for Health and Welfare (THL). The data on reimbursed maternal prescription medicine purchases were obtained from the Register on Reimbursed Drug Purchases, and data on long-term illnesses were obtained from the Register of Entitlements to Reimbursement for Medicine Expenses maintained by the Social Insurance Institution of Finland (Kela). These registers receive information based on a legally compulsory notification request to all health personnel in our country. All recorded diagnoses at FRM are evaluated, classified, and coded by a medical geneticist. If the diagnosis is unclear, more information, including patient records, photographs, radiographs, and specialist opinions, is requested from the involved hospitals, as described in previous publications[17-19]. Multiple national and international investigations have validated the accuracy and high degree of coverage of these data[20-22].

The approval of the institutional review board at the Turku University Hospital was obtained before conducting this study. Also, THL and Kela gave permission to utilize their register data in this study.

Selection of Cases and Controls

The diagnoses in the registers have been coded according to the International Classification of Diseases, Ninth Revision (ICD-9), and ICD, Tenth Revision (ICD-10) during our study period from 1997 to 2016. We searched the FRM for congenital anomalies of the spine including live births, stillbirths, and terminations for fetal anomaly, using diagnostic codes 7561 (ICD-9) or Q76 (ICD-10). All potential cases of vertebral anomaly identified on the basis of such diagnostic codes (see Appendix) were reviewed by 1 author (A.R.). The diagnosis was ascertained from the accompanying written diagnosis text in the FRM, as there are not specific ICD codes for all different types of vertebral anomalies. Problematic cases were further evaluated by 2 pediatric orthopaedic surgeons (J.S. and I.H.). Syndromes and minor anomalies were excluded according to the European network of population-based registries for the epidemiological surveillance of congenital anomalies (European Surveillance of Congenital Anomalies [EUROCAT])[23], based on the recorded diagnoses at the FRM. Lumbosacral agenesis or caudal regression syndrome represents a separate entity that likely has a different etiology from other vertebral anomalies[24], and these cases were therefore excluded. Cases with VACTERL or VATER (vertebral defects, anorectal malformation, tracheo-esophageal fistula, renal anomalies) association (which are defined by the presence of at least 3 of the following malformations: vertebral defects, anorectal malformation, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities[25]) were included in the analysis. Five live-born controls without congenital vertebral deformities, matched by university hospital district and time of birth or termination of pregnancy (within 1 year), were randomly selected from the Medical Birth Register for each case. The selected case-control ratio of 1:5 is considered optimal when the number of cases is limited by the rarity of the disease[26].

The identification of all patients born with congenital spinal malformations in Finland between 1997 and 2016 has been described in detail in a previous publication by some of the authors of this study[6].

Risk Factors

We analyzed the maternal risk factors of age at delivery, body mass index (BMI), parity, history of miscarriages, smoking, chronic diseases, and drug purchases. Maternal weight was recorded systematically at the first prenatal health care visit, at approximately 8 to 10 weeks of pregnancy. Over 99.7% of pregnant women attend maternity health clinics in our country[27]. However, data on maternal BMI have only been collected since 2004 and have been available from all birth hospitals since 2005. Only current smoking during the first trimester was defined as smoking. The maternal pregestational diabetes group contained both type-1 and type-2 diabetes (ICD-10 codes E10, E11, O24.0, and O24.1) diagnosed before conception or during pregnancy. Pregestational diabetes status was also cross-checked using the Register of Entitlements to Reimbursement of Drug Expenses (Kela codes 105 and 215).

Separate analyses for insulin use and pregestational diabetes were not performed, as all mothers with pregestational diabetes in our cohort were also using insulin. All women with a recorded diagnosis of gestational diabetes (O24.4) and/or an abnormal glucose tolerance result were included in the gestational diabetes group.

An initial screening regarding maternal medications was performed using the third level of the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Classification System. Medication groups of interest were selected for analysis if at least 5 mothers among the cases or controls, before the exclusion of syndromic cases, had purchased such medications between 1 month before the last menstrual period and the end of the first trimester. The analyses were then performed in the fourth level of the ATC, with the exception of oral corticosteroids (H02) and insulins (A10A). Because corticosteroids have been previously identified as a risk factor for birth defects in some studies[28] and fast-acting insulins are frequently combined with intermediate-acting or long-acting insulins, those medications were analyzed in the third level of the ATC Classification System. Analyzed long-term illnesses included diabetes, connective-tissue diseases and rheumatoid arthritis (Kela code 202, later referred to as rheumatoid arthritis), and psychotic disorders and other severe mental disorders (Kela code 112, later referred to as psychotic disorders), which included schizophrenia, paranoid personality disorder, mania, bipolar disorder, psychotic depression, and similar disorders.

Statistical Analysis

First, the potential risk factors were evaluated with the Fisher exact test. Then modeling was started with univariate logistic regression suitable for case-control studies, and the STRATA statement was used in coding of matched-pair data in SAS (SAS Institute). Multivariable models were then built by first including all significant factors from the univariate model and then sequentially removing factors that were no longer significant in the multivariable modeling. Maternal age and smoking, known risk factors for several congenital anomalies, were included in all multivariable models. Due to missing values in BMI (which was not collected before 2004 or 2005) and diabetes, sensitivity analyses were performed, when multiple imputation (n = 50) was performed with the fully conditional specification (FCS) method. In the multiple imputation process, case or control status, year of delivery or termination, BMI, diabetes, smoking status, parity, infertility treatment, delivery method, rheumatoid arthritis, and psychosis variables were taken into account (the number of missing values for variables other than BMI and diabetes was minimal).

All statistical tests were 2-sided, with significance set at $p < 0.05$. The analyses were performed using the SAS System, version 9.4 for Windows (SAS Institute).

Source of Funding

This work was supported by research grants from the Clinical Research Institute of Helsinki University Central Hospital (HUCH). The funding and funders had no impact on the content of this study.

Results

A total of 256 cases with a diagnosis of congenital vertebral anomalies were identified in the FRM. We excluded 66 of these because the vertebral anomalies were associated with known syndromes, the most common of which were chromosomal disorders (n = 10), Goldenhar syndrome (n = 8), Klippel-Feil syndrome (n = 7), and spondylocostal dysostosis (n = 7). Additionally, all patients with lumbosacral agenesis (n = 5) were excluded. After exclusions, 190 nonsyndromic cases were included in the study. These congenital vertebral anomaly cases were compared with 950 matched controls.

In univariate analyses, maternal pregestational diabetes (odds ratio [OR], 6.11 [95% confidence interval [CI], 2.26 to 16.48]), rheumatoid arthritis (OR, 27.21 [95% CI, 3.25 to 227.79]), and psychotic disorders (OR, 6.67 [95% CI, 1.49 to 29.79]) were significant risk factors for congenital vertebral anomalies. Similarly, metformin (OR, 7.50 [95% CI 1.25 to 44.89]), heparins (OR, 8.78 [95% CI, 1.58 to 48.75]), estrogens (OR, 6.00 [95% CI, 1.83 to 19.66]), gonadotropins (OR, 2.46 [95% CI, 1.14 to 5.31]), and systemic corticosteroids (OR, 4.00 [95% CI, 1.07 to 14.90]) were associated with increased risk (Table I). Maternal age, BMI, gestational diabetes, other chronic diseases, and parity were not associated with increased risk.

In the multivariable analysis, pregestational diabetes (adjusted OR, 7.30 [95% CI, 2.53 to 21.09]), rheumatoid arthritis (adjusted OR, 22.91 [95% CI, 2.67 to 196.40]), estrogens (adjusted OR, 5.30 [95% CI, 1.57 to 17.84]), and heparins (adjusted OR, 8.94 [95% CI, 1.38 to 57.94]) were significantly associated with an increased risk of congenital vertebral anomaly (Table II).

Sensitivity analyses were performed with imputed values. Maternal smoking was significantly associated with vertebral anomalies (adjusted OR, 1.57 [95% CI, 1.05 to 2.34]), and the other risk factors remained relatively unchanged (Table III).

Discussion

This population-based case-control study demonstrated that maternal pregestational diabetes was a major risk factor for congenital spine deformities. Also, medications often used with assisted reproductive technologies were associated with the risk of vertebral defects: estrogens and heparins in multivariable analysis, and metformin in univariate analysis. In addition, sensitivity analysis using imputed values showed an association with maternal smoking.

Pregestational diabetes is a known risk factor for several congenital malformations[13,29-31], and there is substantial evidence suggesting that hyperglycemia would act as a primary teratogen causing embryonic maldevelopment[32]. In line with our findings, maternal diabetes was found to be a risk factor for congenital spine malformations in a Swedish population-based study[13]. Contrary to their findings, however, we did not observe an increased risk of these defects with gestational diabetes. The prevalence of gestational diabetes was <1% in the Swedish study and around 10% in our study (data not shown), which may reflect a true difference in the baseline risk, but a more plausible explanation is that the diagnostic criteria for gestational diabetes were not comparable across the studies[33].

TABLE I Univariate Analysis of Maternal Risk Factors for Congenital Vertebral Anomalies

Maternal Risk Factors	Cases* (N = 190)	Controls* (N = 950)	OR†
Pregestational diabetes	9 (4.7%)	8 (0.8%)	6.11 (2.26 to 16.48)
Rheumatoid arthritis	6 (3.2%)	2 (0.2%)	27.21 (3.25 to 227.79)
Psychotic disorders	4 (2.1%)	3 (0.3%)	6.67 (1.49 to 29.79)
Primiparity	76 (40.0%)	385 (40.5%)	0.79 (0.57 to 1.10)
Smoking	32 (16.8%)	135 (14.2%)	1.32 (0.83 to 2.10)
Maternal BMI			
<18.5 kg/m^2	1 (0.5%)	28 (2.9%)	0.19 (0.03 to 1.40)
Normal, 18.5 to 24.9 kg/m^2	88 (46.3%)	462 (48.6%)	Reference
25 to 29.9 kg/m^2	22 (11.6%)	155 (16.3%)	0.75 (0.45 to 1.23)
≥30 kg/m^2	16 (8.4%)	98 (10.3%)	0.86 (0.48 to 1.52)
Insulin (A10A)	9 (4.7%)	8 (0.8%)	6.11 (2.26 to 16.48)
Metformin (A10BA)	3 (1.6%)	2 (0.2%)	7.50 (1.25 to 44.89)
Heparins (B01AB)	4 (2.1%)	3 (0.3%)	8.78 (1.58 to 48.75)
Estrogens (G03CA)	6 (3.2%)	5 (0.5%)	6.00 (1.83 to 19.66)
Gonadotropins (G03GA)	10 (5.3%)	21 (2.2%)	2.46 (1.14 to 5.31)
Systemic corticosteroids (H02)	4 (2.1%)	5 (0.5%)	4.00 (1.07 to 14.90)

*The values are given as the number of mothers, with the percentage in parentheses. †The values are given as the unadjusted OR, with the 95% CI in parentheses.

There have been several reports on the maternal use of exogenous sex hormones in early pregnancy and the increased risk of various congenital malformations[31,34-36]. In the current study, estrogens and heparins were associated with congenital vertebral defects. Also, an oral diabetes medication (metformin), which is often used in assisted reproductive technologies, was associated with spinal deformities, but only in univariate analysis. However, the use of assisted reproductive technology was not significantly associated with vertebral anomalies in the current study. It is difficult to establish whether the increased risk of congenital anomalies is attributable to assisted reproductive technology, the medication used, maternal and/or paternal factors related to subfertility, or confounding by indication. Previous studies have also experienced the same challenge[31,37].

The association of maternal use of corticosteroids during pregnancy with congenital malformations has been under debate in previous studies[38,39]. An elevated risk of orofacial clefts has been reported[28]. However, these results have not been replicated by more recent studies[40,41], including on meta-analysis[39]. In the current study, a significant association with congenital vertebral anomalies was observed in univariate analyses but not in multivariable models. Rheumatoid arthritis, a chronic disease often requiring corticosteroid treatment, was significantly associated with vertebral anomalies. However, these findings were based on a small number of exposed mothers. Rheumatoid arthritis has been previously reported to be linked with increased risk of congenital anomalies[42,43].

Maternal smoking is a known teratogen increasing the risk of several congenital anomalies, including heart defects, orofacial clefts, neural tube defects, and gastrointestinal malformations[44]. The role of maternal smoking in the development of congenital spine deformities has been suggested in

TABLE II Multivariable Analysis of Maternal Risk Factors for Congenital Vertebral Anomalies

Maternal Risk Factors	Cases* (N = 190)	Controls* (N = 950)	Adjusted OR†
Pregestational diabetes	9 (4.7%)	8 (0.8%)	7.30 (2.53 to 21.09)
Smoking	32 (16.8%)	135 (14.2%)	1.44 (0.94 to 2.21)
Rheumatoid arthritis	6 (3.2%)	2 (0.2%)	22.91 (2.67 to 196.40)
Heparins (B01AB)	4 (2.1%)	3 (0.3%)	8.94 (1.38 to 57.94)
Estrogens (G03CA)	6 (3.2%)	5 (0.5%)	5.30 (1.57 to 17.84)

*The values are given as the number of mothers, with the percentage in parentheses. †The values are given as the OR adjusted for the other maternal risk factors in the table and maternal age, with the 95% CI in parentheses.

TABLE III Multivariable Sensitivity Analysis of Maternal Risk Factors for Congenital Vertebral Anomalies Using Imputed Values

Maternal Risk Factors	Adjusted OR*
Pregestational diabetes	6.94 (2.40 to 20.00)
Smoking	1.57 (1.05 to 2.34)
Rheumatoid arthritis	27.03 (3.12 to 250.00)
Heparins (B01AB)	8.13 (1.29 to 50.00)
Estrogens (G03CA)	6.33 (1.93 to 20.83)

*The values are given as the OR adjusted for the other maternal risk factors in the table and maternal age, with the 95% CI in parentheses.

experimental studies, but to our knowledge it has not been previously identified as a risk factor in humans[10,45]. Although a significant risk of congenital vertebral anomalies associated with maternal smoking was not identified in our primary analyses, our sensitivity analysis with imputed values suggested an association warranting further studies on the subject.

Although psychosis[46] and schizophrenia[47] have been previously associated with a marginally increased risk of congenital malformations, a recent meta-analysis[48] found no significant increase in the risk of congenital malformations in children prenatally exposed to antipsychotic drugs. Also, a multinational register study that controlled for potential confounders using propensity scores suggested that antipsychotic drugs are not major teratogens[49]. Vertebral anomalies were associated with maternal psychotic disorders in univariate analysis in our cohort, but the number of affected mothers was low among both cases and controls. Furthermore, alcohol abuse disorder is common among patients with schizophrenia[50], and alcohol is a known risk factor for vertebral anomalies[5].

The strength of our study is that the nationwide data on exposures and outcomes were prospectively collected by the universally accessible health-care system. The registries used in this study have been validated as having population-based coverage[18,20,21]. Furthermore, the diagnoses of the congenital vertebral anomalies were confirmed by a medical geneticist.

There were limitations to our study. The data for reimbursed maternal prescription drug purchases at Finnish pharmacies were collected only during the defined exposure window. Thus, we have no information on the possible stockpiling of prescription drugs or on over-the-counter medication, foreign online pharmacies, herbal medicines, or illicit drugs. We also lacked information on the dosage and indications for drugs. Finally, the data on maternal BMI were systematically recorded for only the second half of the study period.

In conclusion, maternal pregestational diabetes and rheumatoid arthritis significantly increased the risk of congenital vertebral anomalies. Similarly, increased risk was observed with maternal smoking and certain maternal medications, many of which are used with assisted reproductive technologies.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org.(http://links.lww.com/JBJS/H542). ■

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