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Association of Pre- and Perinatal Risk Factors With Tourette Syndrome or Chronic Tic Disorders in a Korean School-Age Population

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Objectives: Tic disorders are highly heritable; however, growing evidence suggests that environmental factors play a significant role in their pathogenesis. Studies on these factors have been inconsistent, with conflicting results. Therefore, this study aimed to examine the associations of pre- and perinatal exposure to Tourette syndrome (TS) or chronic tic disorders (CTD) in Korean school-aged children.
Methods: This case-control study used data from a large prospective cohort study. The primary outcome was TS/CTD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria and Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version-Korean Version. Demographic, pre-, and perinatal information was obtained from the maternal questionnaires. Data between the TS/CTD and control groups were compared using the chi-squared or Student's t-test, as appropriate. Two-step logistic regression analyses were used to test the association between TS/CTD and pre- and perinatal risk factors.
Results: We included of 223 children (78 with TS/CTD and 145 controls). Significant differences in the demographic data between the two groups were observed. The male sex ratio, mean parental age, parental final education level, and family history of tics were included as confounders. In the final adjusted multivariable model, TS/CTD was significantly associated with antiemetic exposure during pregnancy (odds ratio [OR]=16.61, 95% confidence interval [CI] 1.49–185.22, p=0.02) and medically assisted reproduction (OR=7.89, 95% CI 2.28–27.28, p=0.01).
Conclusion: Antiemetic exposure and medically assisted reproduction are significantly associated with the risk of TS/CTD. These results should be replicated in future prospective and gene-by-environment studies.

Keywords: Chronic motor or vocal tic disorder; Delivery, Obstetric; Etiology; Pregnancy; Prenatal Exposure Delayed Effects; Risk factors; Tourette disorder

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INTRODUCTION

Tic disorders are childhood-onset neurodevelopmental disorders characterized by a wide range of clinical manifestations depending on the type and duration of tics. Tourette syndrome (TS) is diagnosed when multiple motor tics and one or more vocal tics have been present for more than one year, whereas chronic tic disorder (CTD) is diagnosed when only one type (either motor or vocal but not both) of tic has been present for more than one year [1]. The unique nature of the clinical course makes TS and CTD highly heterogeneous and complex. The age of onset is typically 4–6 years, reaching peak severity at approximately 10–12 years of age. Following a gradual decline after its peak, symptoms improve significantly and complete remission is possible by early adulthood [2]. Furthermore, the severity and frequency of tics wax and wane along the course with various exacerbating and alleviating factors [2,3]. For these reasons, a wide range of prevalence has been reported for TS and CTD, depending on the studies' sample sizes, study populations, diagnostic criteria, and methodologies [4-7]. A recent systematic review and meta-analysis reported a population prevalence of 0.52% for TS [5] and 1.61% for CTD in the general

school-age population [6]. Moreover, a marginally lower prevalence of TS and CTD has been reported in the Korean school-age population (0.27% and 1.42%, respectively) [8].

The etiology of TS is highly complex and multifactorial [9]. Several twin and family studies as well as recent advances in genetic studies have established that TS has a strong genetic component with high heritability and polygenic inheritance [2,10]. However, despite the high heritability estimate of 77% reported in a recent family study, the authors concluded that non-shared environmental factors may explain the remaining non-genetic component of the etiology [11]. Therefore, complex interactions between polygenic and environmental factors have been suggested to account for such heterogeneous clinical manifestations and the complex etiology of TS.

Since the idea of non-genetic factors contributing to the pathophysiology of TS was first speculated, a large number of studies have investigated the potential environmental factors with particular attention to pre- and perinatal risk factors [12]. Maternal smoking, alcohol consumption, cannabis exposure during pregnancy, birth weight, gestational age, parity, number of prenatal visits, cesarean section, delivery complications, Apgar scores at 5 min after birth, younger maternal age, and older paternal age are reportedly associated with the onset of TS [13-20]. Other studies have also reported the association of various pre- and perinatal factors with increased tic severity and common comorbidities, namely attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) [21-23]. While these findings have undoubtedly highlighted the associations between environmental factors and the pathogenesis of TS, the results have been inconsistent. These studies were often limited by poor-quality methodology, including inappropriate statistical analyses, lack of control groups, and limited number of factors investigated [12,15]. Furthermore, to our knowledge, no study has explored these potential risk factors in a Korean population, where genetic and cultural backgrounds differ from those in Western and other Asian populations. Therefore, this study aimed to examine the association of clinically diagnosed TS and CTD with exposure to various pre- and perinatal risk factors in school-age children in Korea. Based on the existing evidence, we hypothesized that the pre- and perinatal risk factors reported in the literature, as well as any novel adverse exposures that could potentially impact the brain's neurocircuit development during this period, would be associated with TS and CTD in this population.

METHODS

Participants

This case-control study utilized data from a large prospective cohort study to develop diagnostic and evaluation techniques using biomarkers based on brain networks in neurodevelopmental disorders. This study was granted ethical approval by the Institutional Review Board of the Medical Research Ethics Committee of the Seoul National University Hospital (SNUH) (IRB no: 1507-118-690, 2008-116-1150). The cases and controls were selected from the original cohort enrolled between January 2016 and December 2020. For the TS/CTD group, 6–18-year-old children attending the child and adolescent psychiatry clinic of a university-affiliated hospital (SNUH) were eligible. The inclusion criteria were clinical diagnosis of TS or CTD, no other psychiatric comorbidities, no previous medication or less than 1 year duration of medication and having been medication-free in the 4 months preceding enrolment, and an intelligence quotient (IQ) of 70 or above. For the control group, advertisements for recruitment were posted throughout the hospital and regional community mental health service centers. The range of eligible age for the control group in the original cohort included marginally lower age (2–18 years old) compared to the TS/CTD group (6–18 years old). Despite this eligible age difference, the original cohort's control group was used to prevent potential selection biases, and any resulting mean age difference between the two groups was to be included as a confounder in the analyses. Other inclusion criteria were the absence of clinical diagnoses of any neuropsychiatric disorder or evidence of prominent developmental delay, and an IQ of 70 or above. Children with diagnoses of congenital genetic disorder, acquired brain injury including cerebral palsy, convulsive or other neurological disorders, schizophrenia, psychotic disorder, depressive or bipolar disorder, obsessive-compulsive disorder, language or severe learning disorder, and an IQ of less than 70 were excluded. A clearly written information booklet explaining the purpose and design of the study was provided, and a written informed consent form was signed by both the participants and their parents.

Primary outcome

The primary outcome of the study was the diagnosis of TS or CTD based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria [1] and Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version- Korean Version (K-SADS-PL-K). The K-SADS-PL is a semi-structured interview developed by Kaufman et al. [24] to determine the diagnosis and severity of 32 child-adolescent psychiatric disorders at present, as well as during the lifetime of the interviewee. The Korean version has robust reliability and validity in diagnosing major child psychiatric disorders, including TS and CTD [25].

All participants were assessed by child and adolescent psychiatrists working at the hospital when they were first enrolled. Those who met either the DSM-5 criteria or the diagnostic threshold of the K-SADS-PL-K for TS or CTD were eligible for the TS/CTD group. Participants recruited for the control group were also examined using these criteria to exclude any potentially undiagnosed psychiatric disorders, including TS and CTD.

Predictor variables

Predictor variables were defined as potential prenatal and perinatal exposures associated with the onset, severity, and comorbidities of TS, as previously reported in the literature. In addition, any relevant exposures potentially involved in the pathogenesis of other neurodevelopmental disorders were included for comprehensive exploratory purposes. Information about the predictor variables was obtained through maternal questionnaires at the time of enrollment. These questionnaires comprised five sections: demographics, parental health status, pregnancy, delivery, and child's development. For this study, information regarding demographic data and pregnancy- and delivery-related events was extracted. For demographic data, age, sex, parental age and education level, socioeconomic status (SES), and family history of tics were included as potential covariates. Parental final education levels were selected as more accurate measures of SES over self-rated SES on a five-point scale with scores ranging from low to high, and the SES data were excluded from the covariates. In terms of prenatal exposure, the categorical variables examined were parity (first born vs. second or later child), miscarriage/abortion/stillbirth, medically assisted reproduction, intermittent/no antenatal visit, severe hyperemesis, negative pregnancy reaction, substance exposure during pregnancy (alcohol, tobacco, coffee, others as separate variables), medication exposure during pregnancy (any, antiemetics, antihypertensives, miscarriage preventive medications, weight loss medications, vitamins, and over-the-counter medications), and pregnancy complications (any, fetal position, preterm/premature rupture of membrane, vaginal bleeding, psychosocial stress, minor complications including constipation/lumbar pain/perineal infection/dyspepsia, etc.). The continuous variables were paternal and maternal age at pregnancy. With regard to perinatal exposures, all variables were categorical with preterm (<37 weeks of gestation), post-term (>42 gestational weeks), twin delivery, instrumental delivery (including forceps or vacuum), cesarean section, low birth weight (<2500 g), use of incubator, maternal postpartum depression, and delivery complications (any, dystocia, umbilical cord complications, placental complications, and fetal cardiopulmonary complications as separate variables).

Analyses

The differences between the TS/CTD and control groups in terms of demographic and predictor variables data were compared using the chi-squared or Fisher's exact test as appropriate for categorical variables and Student's t-test for continuous variables. A two-step approach was adopted for further analyses of the association between TS/CTD and predictor variables. First, unadjusted univariable analyses were performed using binary logistic regression with the diagnosis of TS/CTD as the dependent variable and each potential risk factor as an independent variable. Any significant differences in demographic data between the two groups were included as covariates in the adjusted univariable analyses for each predictor variable.

For the second step of the analyses, predictor variables that exhibited trend-level ($p<0.10$) associations in the adjusted univariable analyses were pooled into the final multivariable logistic regression model along with potential covariates. Demographic data including sex, parental age, parental final education level, and family history of tics were also examined as confounders in the final model. Predictor variables that reached a statistically significant level in the final multivariable model were interpreted as putative risk factors for the diagnosis of TS or CTD. Finally, a post-hoc analysis was performed with a duration of maternal smoking longer than 10 years as an additional predictor variable in the final model to compensate for negative maternal smoking during pregnancy results in the entire sample. An arbitrary cutoff point of 10 years was determined by taking into account the mean ages of both groups; if the mother had smoked for longer than her child's age, a higher chance of tobacco exposure during pregnancy could be posited.

All statistical analyses were performed using IBM-SPSS version 26.0 (IBM Corp., Armonk, NY, USA), and the results of two-tailed tests were considered statistically significant at p values less than 0.05. Missing data were coded as missing values in the analyses. For the final multivariable logistic regression, Hosmer-Lemeshow and Nagelkerke tests were used to determine the goodness-of-fit of the data. The results of univariable and multivariable logistic regression analyses were presented as odds ratios (ORs) with 95% confidence intervals (CIs).

RESULTS

Demographic characteristics

A total of 243 eligible participants were identified from the original cohort. After the initial assessment, 18 children without pre- and perinatal data and two children who did not meet the inclusion criteria were excluded. The final sample

of 223 children, consisting of 78 with TS or CTD and 145 without tic disorders, was available for the study. Statistically significant differences in sex, mean parental age, parental final education levels, SES, and family history of tics were found between the two groups. The TS/CTD group had a significantly higher male ratio (71.8%) than the control group (56.6%) (p=0.03) (Table 1). Moreover, the same group had lower mean paternal and maternal ages of 46.53±4.35 vs. 49.73±5.62 (p<0.01) and 43.42±4.64 vs. 47.12±4.86 (p<0.01), respectively, compared to those of the control group. The final education level for both parents was significantly higher in the TS/CTD group (university degree or higher, p<0.01), as was the self-rated SES (high, p<0.01). Lastly, the prevalence of a family history of tics was significantly higher in the TS/CTD group, as expected (p<0.01). The differences in demographic data between the two groups are summarized in Table 1.

Univariable analyses

In univariable analyses, all potential pre- and perinatal risk factors were examined first without adjustments for covariates. These analyses were then repeated for each risk factor, with sex, parental age, parental final education level, and family history of tics as covariates in the adjusted analyses. For prenatal risk factors, both parity (second or later born) and previous miscarriage/abortion/stillbirth showed trend-level associations with a reduced risk of TS or CTD in the unadjusted analyses (OR=0.57, 95% CI 0.31–1.04, p=0.07; OR=0.56, 95% CI 0.30–1.07, p=0.08, respectively) (Table 2). However, these associations were no longer significant after adjusting for the covariates. In contrast, negative reactions to pregnancy showed a trend-level association with an increased risk of TS/CTD, but was no longer significant after adjusting for the covariates (Table 2). Medically assisted reproduction showed a strong association with a high OR for TS/CTD in the unadjusted analysis and remained significant after adjustment, although the magnitude of OR was slightly reduced (OR=13.66, 95% CI 5.33–35.01, p<0.01, and OR=9.57, 95% CI 3.34–27.41, p<0.01, respectively). Notably, both older paternal and maternal age at pregnancy were nominally associated with a higher risk of TS/CTD only after adjusting for covariates (most likely parental age). Lastly, exposure to antiemetics for severe hyperemesis during pregnancy was significantly associated with an increased risk of TS/CTD in the unadjusted analysis. However, this association was attenuated to trend-level significance after adjustment (OR=7.42, 95% CI 1.53–35.91, p=0.01 and OR=5.14, 95% CI 0.95–27.71, p=0.06, respectively).

Perinatal risk factors failed to show significant associations with the risk of TS or CTD, except for the two exposures. Incubator use immediately after birth was associated with a high OR for TS or CTD in the unadjusted analysis, and this association remained largely unchanged after adjusting for the covariates (OR=4.32, 95% CI 1.42–13.16, p=0.01; OR=4.46, 95% CI 1.22–16.26, p=0.02, respectively). Interestingly, cesarean delivery originally showed no significant association with the risk of TS/CTD in the unadjusted analysis, but a trend-level association was noted after adjusting for the covariates (OR=2.06, 95% CI 0.96–4.37, p=0.06).

Table 1. Demographic comparison between control and TS/CTD group

	Control (n=145)	TS/CTD (n=78)	p value
Age (year)	9.16±3.16	9.09±2.30	0.85†
Sex, male	82 (56.6)	56 (71.8)	0.03
Paternal age (year)	49.73±5.62	46.53±4.35	<0.01
Maternal age (year)	47.12±4.86	43.42±4.64	<0.01
Paternal education level			
Degree or higher	93 (66.4)	68 (90.7)	<0.01
High school	44 (31.4)	7 (9.3)	<0.01
Middle school	3 (2.1)	0 (0.0)	0.55‡
Primary school	0 (0)	0 (0)	NA
No formal education	0 (0)	0 (0)	NA
Maternal education level			
Degree or higher	77 (54.6)	64 (86.5)	<0.01
High school	43 (30.5)	10 (13.5)	<0.01
Middle school	2 (1.4)	0 (0)	0.55‡
Primary school	3 (2.1)	0 (0)	0.55‡
No formal education	16 (11.3)	0 (0)	<0.01
SES*			
High	13 (9.1)	19 (24.7)	<0.01
Middle	72 (50.3)	42 (54.5)	0.57
Low	58 (40.6)	16 (20.8)	<0.01
Family history			
Tic disorder	4 (3.0)	14 (18.2)	<0.01

Data are presented as mean±standard deviation or n (%). *SES was originally self-rated according to 5 different levels but data was combined to represent three levels for the purpose of analyses; †Equal variances not assumed; ‡Fisher's exact test. TS, Tourette syndrome; CTD, chronic tic disorders; SES, socioeconomic status

Multivariable analyses

In this final model, the demographic variables of male sex and a family history of tics remained nominally significant (OR=2.89, 95% CI 1.12–7.44, p=0.03 and OR=5.57, 95% CI 1.31–23.69, p=0.02, respectively), but parental age and parental education level were no longer associated with TS or CTD. In terms of pre- and perinatal risk factors, medically assisted reproduction (OR=7.89, 95% CI 2.28–27.28, p=0.01) and antiemetic exposure during pregnancy (OR=16.61, 95% CI 1.49–185.22, p=0.02) consistently exhibited significant

associations in this final model (Table 3). Both assisted reproduction and antiemetic exposure increased the odds of TS/CTD by 8–17-fold. In terms of post-hoc analysis, maternal smoking duration longer than 10 years exhibited no significant association with TS/CTD in the final multivariable model (OR=1.36, 95% CI 0.10–18.91, p=0.82), whereas other significant predictor variables except sex remained largely unchanged with family history of tics (OR=5.92, 95% CI 1.11–

Table 2. Univariable logistic regression of potential risk factors of Tourette syndrome or chronic tic disorders

Exposure	Unadjusted		Adjusted*	
	OR (95% CI)	p	OR (95% CI)	p
Prenatal risk factors				
Parity	0.57 (0.31–1.04)	0.07	0.67 (0.31–1.41)	0.29
Miscarriage, abortion, stillbirth	0.56 (0.30–1.07)	0.08	0.76 (0.35–1.64)	0.49
Assisted reproduction	13.66 (5.33–35.01)	<0.01	9.57 (3.34–27.41)	<0.01
Paternal age at pregnancy	1.06 (0.99–1.14)	0.11	1.26 (1.11–1.44)	<0.01
Maternal age at pregnancy	1.03 (0.95–1.10)	0.51	1.33 (1.15–1.54)	<0.01
Intermittent or no antenatal visit	1.20 (0.63–2.32)	0.58	1.15 (0.52–2.54)	0.74
Hyperemesis	0.86 (0.49–1.50)	0.60	0.95 (0.48–1.88)	0.88
Negative pregnancy reaction	1.73 (0.99–3.03)	0.06	1.22 (0.62–2.42)	0.57
Substance exposure, any	1.27 (0.69–2.33)	0.44	0.95 (0.46–1.94)	0.88
Alcohol	3.56 (0.64–19.89)	0.15	3.21 (0.46–22.54)	0.24
Smoking	N/A		N/A	
Coffee	1.18 (0.62–2.24)	0.61	0.85 (0.40–1.82)	0.68
Other substances	1.77 (0.55–5.70)	0.34	2.01 (0.51–7.95)	0.32
Medication exposure, any	1.20 (0.68–2.13)	0.53	1.01 (0.50–2.04)	0.98
Hyperemesis	7.42 (1.53–35.91)	0.01	5.14 (0.95–27.71)	0.06
Antihypertensive	N/A		N/A	
Miscarriage	1.01 (0.35–2.91)	0.98	0.60 (0.17–2.07)	0.41
Weight gain	N/A		N/A	
OTC	1.23 (0.69–2.22)	0.49	1.03 (0.50–2.09)	0.95
Pregnancy complications, any	1.59 (0.86–2.94)	0.14	1.41 (0.67–2.98)	0.36
Fetal position	1.39 (0.52–3.69)	0.51	1.03 (0.35–3.04)	0.95
PROM	2.02 (0.81–5.00)	0.13	1.45 (0.45–4.67)	0.53
Vaginal bleeding	0.66 (0.31–1.43)	0.29	0.64 (0.16–2.52)	0.52
Minor complications†	2.10 (0.62–7.11)	0.24	3.57 (0.75–16.87)	0.11
Psychological stress	1.56 (0.87–2.79)	0.13	1.40 (0.69–2.84)	0.35
Perinatal risk factors				
Preterm	1.28 (0.35–4.67)	0.24	1.03 (0.26–4.14)	0.97
Post-term	1.75 (0.61–5.03)	0.30	1.46 (0.43–4.96)	0.55
Twin	0.60 (0.12–3.04)	0.54	N/A	
Assisted delivery	1.36 (0.61–3.02)	0.46	0.97 (0.35–2.71)	0.96
Cesarean	1.21 (0.68–2.16)	0.52	2.06 (0.96–4.37)	0.06
LBW	1.42 (0.47–4.24)	0.54	0.84 (0.19–3.67)	0.81
Incubator	4.32 (1.42–13.16)	0.01	4.46 (1.22–16.26)	0.02
Maternal depression	1.06 (0.57–1.98)	0.85	1.29 (0.59–2.80)	0.52
Delivery complications, any	0.91 (0.43–1.94)	0.82	0.90 (0.37–2.16)	0.81
Dystocia	0.46 (0.14–1.44)	0.18	0.57 (0.16–2.04)	0.39
Umbilical cord problem	1.75 (0.34–8.90)	0.50	3.03 (0.42–21.65)	0.27
Placental problem	1.74 (0.34–8.83)	0.51	1.03 (0.18–5.95)	0.98
Cardiopulmonary complication	N/A		N/A	

*adjusted for sex, paternal age, maternal age, paternal education level, maternal education level, family history of tics; †constipation, lumbar pain, perineal infection, dyspepsia etc. OR, odds ratio; CI, confidence interval; OTC, over the counter drugs; PROM, premature rupture of membrane; LBW: low birth weight

Table 3. Multivariable adjusted logistic regression model of risk factors for tic disorders

Exposure	Adjusted OR (95% CI)	p
Sex, male	2.89 (1.12−7.44)	0.03
Paternal age	0.94 (0.64−1.39)	0.76
Maternal age	0.80 (0.53−1.22)	0.30
Paternal education level	2.69 (0.76−9.44)	0.12
Maternal education level	2.35 (0.82−6.72)	0.11
Family history of tics	5.57 (1.31−23.69)	0.02
Assisted reproduction	7.89 (2.28−27.28)	0.01
Paternal age at pregnancy	1.13 (0.75−1.70)	0.56
Maternal age at pregnancy	1.18 (0.76−1.81)	0.47
Hyperemesis medication exposure	16.61 (1.49−185.22)	0.02
Cesarean delivery	1.36 (0.52−3.59)	0.54
Incubator usage	0.91 (0.16−5.12)	0.92

All variables are mutually adjusted for each other in the model. Nagelkerke R^2, p=0.56; Hosmer-lemeshow, p=0.46. This model classified 78.0% of the population (22% missing cases, 83.3% tic group, 75.2% control group). OR, odds ratio; CI, confidence interval

31.57, p=0.04), assisted reproduction (OR=12.48, 95% CI 2.80−55.58, p=0.01), and antiemetic exposure during pregnancy (OR=13.88, 95% CI 1.16−166.09, p=0.038) were still significantly associated with TS/CTD in this model.

Sensitivity analysis

As mentioned earlier, the control group in this study had a marginally wider range of age inclusion criteria of 2−18 years as opposed to 6−18 years for the TS/CTD group. Given the typical onset of tic disorders at 4−6 years of age, the possibility of younger participants in the control group potentially developing tic symptoms at a later stage was considered. The results of the final multivariable model remained largely unchanged after excluding 15 participants below the age of 6 years in the control group. Male sex and family history of tics continued to show significant associations with TS/CTD (OR=4.10, 95% CI 1.30−12.91, p=0.016 and OR=5.22, 95% CI 1.00−27.32, p=0.050, respectively), assisted reproduction (OR=8.09, 95% CI 1.77−36.93, p=0.007), and antiemetic exposure (OR=16.52, 95% CI 1.22−223.13, p=0.035) in terms of predictor variables. Similarly, no other variables in the model exhibited nominally significant associations with the TS/CTD.

DISCUSSION

The results of this study demonstrate that early life exposure, even as early as conception, is significantly associated with the risk of tic disorders. After adjusting for relevant confounders, antiemetic exposure during pregnancy, and medically assisted reproduction were the only risk factors associated with TS or CTD. Tic disorders are highly heritable condition supported by the previous genetic studies [2,10] and significantly higher family history of tics in TS/CTD group in this study. The male preponderance in the TS/CTD group in our study conforms with most of the previous prevalence studies reporting a male-to-female ratio of approximately 3 to 4:1 [4,6], which also supports the notion of a high genetic component of tic disorders. However, growing evidence suggests environmental factors play a significant role in the pathogenesis of tic disorders as mentioned earlier [9,12,26]. Among the myriad potential environmental factors, this study failed to show any significant associations between TS/CTD and parental age or educational level. This is consistent with the findings of a recent systematic review and meta-analysis by Chao et al. [12], who concluded that the majority of results for the demographic factors of parents were not associated with the risk of TS [12]. Regarding the prenatal risk factors found in this study, previous studies have reported associations between maternal medication use during pregnancy and the severity of TS or comorbid ADHD/OCD [13,21] but not many have reported an association with the risk of tic disorders. One case-control study reported that severe hyperemesis requiring medical attention was significantly associated with the presence of CTDs compared with unaffected controls [27]. This conforms with the findings of this study, wherein exposure increased the risk of TS/CTD by approximately 16- to 17-fold. However, this result should be interpreted with caution, as the number of mothers exposed to antiemetics during pregnancy was relatively small, resulting in a wide 95% CI, suggesting that the sample size might have been underpowered. Despite this, the abovementioned study had a total sample size of 1113 participants with 586 children with CTD, which is a remarkably larger sample size than this study [27]. Another significant finding in this study, which has not been reported before, was that children born after assisted reproduction therapy were significantly associated with a higher risk of TS/CTD than were spontaneously conceived children. Few studies have assessed neurodevelopmental outcomes in this population, with inconsistent results. However, one prospective register-based cohort study also found that the risk of tic disorders was higher in children born after fertility treatment than that in spontaneously conceived children, which is consistent with the findings of this study [28].

Notably, the sample of this study exhibited no significant associations between all other previously reported pre- and perinatal risk factors with TS/CTD. These findings are further supported by previous studies that found no significant association between maternal smoking [15,17,18,27], low birth weight [15,18,27], gestational age [15,18], and delivery com-

plications [15,27]. In this study, parity, previous miscarriage/abortion/stillbirth, and negative reactions to pregnancy all exhibited trend-level associations with TS/CTD, but were no longer significant after the adjustments for confounders. These findings suggest that the previously reported associations between these factors might have been confounded by unmeasured demographic variables. Interestingly, cesarean delivery was no longer a significant risk factor in the final adjusted model, which incorporated maternal age at pregnancy as a covariate. A study that reported a significant association did not consider maternal age at pregnancy as a potential confounder, which might have affected their results [14].

These early adverse exposures are thought to exert "organizational effects" on the development of brain networks involved in the clinical manifestations of tics. Numerous environmental factors can potentially significantly affect the organization of crucial neural pathways involved in the pathogenesis of tic disorders [9]. Although the mechanisms involved in each of these individual environmental factors remain to be elucidated, recent studies have suggested putative epigenetic mechanisms underlying these complex and dynamic interactions [26]. Epigenetic modifications through DNA methylation and histone modifications occur throughout development before acquiring adult profiles of the genome, and these modifications are influenced by constantly changing environmental factors [26]. Therefore, these modifications can alter the expression of genes involved in crucial neural circuits (i.e., cortico-striato-thalamo-cortical circuits) and neurotransmitters (dopamine, glutamate, GABA, etc.) that are considered to play major roles in the pathogenesis of tic disorders [2].

Strengths and limitations

This study examined a wide range of potential pre- and perinatal risk factors involved in the pathogenesis of tic disorders. To our knowledge, this is the first comprehensive study to examine such a number of risk factors in Korean school-age children. Furthermore, several important confounders that could have influenced the interpretation of the results were considered in our analyses, including genetic factors (sex and family history of tics). Our two-step analyses allowed us to identify each risk factor and incorporate it into a single model that mutually adjusted for potential confounding with one another. Nevertheless, this study had a few limitations. First and most importantly the study was retrospective, with pre- and perinatal information obtained from maternal questionnaires being subject to recall biases. However, Rice et al. [29] compared the agreement between maternal reports and antenatal records for a range of pre- and perinatal factors and concluded that maternal reports were accurate for most of these events [29]. Similarly, Chao et al. [12] also reported no difference in strength of association between studies using birth certificate data and maternal retrospective recall memory. Second, none of the mothers answered "yes" to smoking exposure during pregnancy, which limited our ability to analyze this highly debated risk factor in this population. One study found a significant discrepancy between self-reported and chemically verified (cotinine) smoking prevalence among Korean women, with more than half of smoking women underreporting in self-reports [30]. This underestimation is most likely due to the stigma of female smokers viewed as socially unacceptable in Korean culture [30]. Furthermore, the underreporting of mothers, especially self-preventable adverse exposures during pregnancy, could have been a major source of discrepancy, if any, rather than a recall bias, in populations from Korean or similar cultures. We attempted to compensate for this limitation by conducting a post-hoc analysis using maternal health behavior data obtained from the original cohort, which yielded no significant association with the risk of TS/CTD. Lastly, uncovering the underlying mechanisms for these risk factors in the pathogenesis of tic disorders was beyond the scope and design of this study.

CONCLUSION

This case-control study in Korean school-age children demonstrated the potential prenatal risk factors for TS or CTD. Antiemetic exposure during pregnancy and medically assisted reproduction were significantly associated with TS/CTD in the final adjusted model. Further prospective studies comparing the risk factors in two different clinical and community-based samples are needed to confirm these results. In addition, well-designed gene-by-environment and epigenetic studies with large sample sizes are warranted to investigate the complex pathophysiology of tic disorders.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Byung-Nyun Kim, Soon-beom Hong, Johanna Inhyang Kim, Jung Lee. Data curation: Wooseok Choi, Soon-beom Hong, Johanna Inhyang Kim, Jung Lee, Sumin Kim, Mee Rim Oh. Formal analysis: Wooseok Choi, Soomin Jang, Yebin D Ahn, You Bin Lim. Funding acquisition: Bung-Nyun Kim, Soon-beom Hong, Johanna Inhyang Kim, Jung Lee, Sumin Kim, Mee Rim Oh. Investigation: Wooseok Choi, Soomin Jang, Yebin D Ahn. Methodology: Bung-Nyun Kim, Wooseok Choi, Soomin Jang, Yebin D Ahn, You Bin Lim. Project administration: Bung-Nyun Kim, Soon-beom Hong, Johanna Inhyang Kim, Jung Lee, Soomin Jang, Yebin D Ahn, You Bin Lim, Sumin Kim, Mee Rim Oh. Resources: Bung-Nyun Kim,

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