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Preliminary study of environmental risk and protective factors during pregnancy for cleft lip with or without palate in the Korean population

Min-Jeong Kang[a]
Nang Paung Li[a]
Hyunseung Hong[b]
Hyo-Sang Park[a]
Ji Wan Park[c]
Marie M. Tolarova[d]
Il-Hyung Yang[e]
Mihee Hong[a,f]
Seung-Hak Baek[e]

[a]Department of Orthodontics, School of Dentistry, Kyungpook National University, Daegu, Korea
[b]Department of Orthodontics, School of Dentistry, Seoul National University, Seoul, Korea
[c]Department of Medical Genetics, Hallym University College of Medicine, Chuncheon, Korea
[d]Department of Orthodontics, Arthur A. Dugoni School of Dentistry, University of the Pacific, San Francisco, CA, USA
[e]Department of Orthodontics, School of Dentistry, Dental Research Institute, Seoul National University, Seoul, Korea
[f]Department of Orthodontics, School of Dentistry, Translational Research in Dentistry, Kyungpook National University, Daegu, Korea

Objective: To investigate which types of environmental exposure during pregnancy are risk and protective factors for cleft lip with or without cleft palate (CL/P). **Methods:** This case-control study included 278 orthodontic patients with CL/P (CL/P group) and 51 without CL/P (non-CL/P group). Demographic and environmental exposure data were collected using questionnaires completed by the parents. Statistical analyses were performed to identify the potential risk and protective factors for CL/P. **Results:** The two groups did not show significant difference in (1) body weight at birth and number of previous births; (2) fathers' ages at birth and occupation; (3) parents' chronic diseases, alcohol consumption, and exposure to harmful substances; and (4) mothers' smoking, secondhand smoking, and vitamin and calcium intake. Most patients with CL/P were born at normal term (≥ 37 weeks, 93.2%) with normal body weight (2.9–3.7 kg, 63.7%) and as either the first or second child (90.3%). In the CL/P group, the percentages of mothers who were very young or old (≤ 19 years, ≥ 40 years) and with physical labor in their occupation were low (1.8% and 2.2%, respectively). Compared with the non-CL/P group, the CL/P group showed a lower percentage of maternal folic acid intake (68.6% vs. 20.9%, odds ratio [OR] = 0.121; $P < 0.001$) and higher percentages of mothers' drug intake and fathers' smoking habits (3.9% vs. 16.2%, OR = 4.73, $P < 0.05$; 39.2% vs. 61.2%, OR = 2.44, $P < 0.01$). **Conclusions:** The findings of this study may explain the association between environmental factors and CL/P risk.

Key words: CL/P, Environmental factor, Folic acid intake, Smoking

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Corresponding author: Mihee Hong.
Associate Professor, Department of Orthodontics, School of Dentistry, Translational Research in Dentistry, Kyungpook National University, 2175 Dalgubeol-daero, Jung-gu, Daegu 41940, Korea.
Tel +82-53-600-7374 e-mail mhhong1208@gmail.com

Corresponding author: Seung-Hak Baek.
Professor, Department of Orthodontics, School of Dentistry, Dental Research Institute, Seoul National University, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Tel +82-2-6256-3238 e-mail drwhite@snu.ac.kr

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INTRODUCTION

Among livebirths in Korea in 2005–2006, Kim et al.[1] reported that the five major birth defects were atrial septal defect, ventricular septal defect, hydronephrosis, patent ductus arteriosus, and cleft lip with or without cleft palate (CL/P). The prevalence of CL/P in Korea is 1:550–1:1,000 in newborns.[1-3] Owing to problems associated with facial appearance, speech, and malocclusion in patients with CL/P, orthodontists are involved in its long-term multidisciplinary management from birth to the completion of facial growth.[4,5]

CL/P is a complex birth defect arising from an interaction between genetic predisposition and environmental exposure during the critical period of embryonic development, particularly between 6 and 12 weeks of gestation.[6,7] While the exact mechanisms remain unclear, previous studies have underscored the role of various environmental factors. A systematic review and meta-analysis by Lee et al.[6] reported significant associations between maternal exposure to environmental factors and congenital anomalies, including CL/P and congenital heart disease. The suggested environmental factors were as follows: exposure to air pollution and toxic chemicals, parental smoking, maternal history of infections during pregnancy, pre-gestational and gestational diabetes mellitus, maternal obesity, maternal drug intake, conception via assisted reproductive technologies, and socioeconomic factors.[6] Conversely, adequate intake of folic acid, vitamins, and calcium might have protective effects against CL/P.[6,8-10]

Despite the recognized impact of environmental factors on the prevalence of CL/P, comprehensive research on specific risk or protective factors within the Korean population is scarce. The understanding of these factors is crucial for the development of effective preventive strategies. Therefore, the purpose of this retrospective survey study was to investigate which types of environmental exposure during pregnancy are risk and protective factors for CL/P in the Korean population.

MATERIALS AND METHODS

Participants

This case-control study included 278 orthodontic patients with CL/P (the CL/P group) and 51 without CL/P (the non-CL/P group) who visited Seoul National University Dental Hospital (SNUDH) and Kyungpook National University Dental Hospital (KNUDH) until December 2023. The CL/P group consisted of 161 boys and 117 girls: 58 with cleft lip with or without cleft alveolus (CL/A), 176 with cleft lip and palate (CLP), and 44 with cleft palate only (CPO) (Table 1). SNUDH contributed 57 patients with CL/A, 31 patients with CPO, 160 patients with CLP, and 21 control patients, while KNUDH contributed 12 patients with CPO, 18 patients with CLP, and 30 control patients. The composition of CL/P patients showed a significantly higher prevalence of females in the CP group than in the other groups and a significantly higher prevalence of males in the CLP group than in the other groups ($P < 0.001$; Table 1). Fifty-one non-CL/P orthodontic patients without pathological diseases or syndromes were recruited as the control group (27 boys and 24 girls; Table 2).

Questionnaire survey

Data were collected retrospectively using questionnaires answered by the parents of the participants. Both institutes used the same questionnaire. The questionnaire consisted of three parts: (1) demographic information including patient sex, gestational duration, body weight at birth, number of previous births and cleft type, parents' age at birth, and occupation; (2) maternal medical and environmental information including chronic disease, medication drug intake, smoking, secondhand smoking, alcohol consumption, exposure to harmful substances, and vitamin, folic acid, and calcium intake; and (3) paternal medical and environmental in-

Table 1. Distribution of cleft type and sex in the CL/P group

		Sex		*P* value
		Male	Female	
Cleft type	CPO (n = 44)	14 (31.8)	30 (68.2)	< 0.001***
	CL/A (n = 59)	34 (57.6)	25 (42.4)	
	CLP (n = 175)	113 (64.6)	62 (35.4)	
Total (n = 278)		161 (57.9)	117 (42.1)	

Values are presented as number (%).
Chi-square test was performed.
CL/P, cleft lip with or without cleft palate; CPO, cleft palate only; CL/A, cleft lip with or without cleft alveolus; CLP, cleft lip and palate.
***$P < 0.001$.

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Table 2. Demographic data of the subjects

		CL/P group	Non-CL/P group	*P* value†
Sex†	Male	161 (57.9)	27 (52.9)	0.510
	Female	117 (42.1)	24 (47.1)	
Body weight at birth (kg)†	≤ 2.4	18 (6.5)	6 (11.8)	0.587
	2.5–2.9	50 (18.0)	6 (11.8)	
	2.9–3.7	177 (63.7)	32 (62.7)	
	3.7–4.1	27 (9.7)	6 (11.8)	
	≥ 4.2	6 (2.2)	1 (2.0)	
Gestational duration (wk)†	≤ 32	2 (0.7)	6 (11.8)	< 0.001***
	33–36	17 (6.1)	6 (11.8)	
	≥ 37	259 (93.2)	39 (76.5)	
Number of previous births before subjects†	0	135 (48.6)	29 (56.8)	0.783
	1	116 (41.7)	17 (33.3)	
	2	25 (9.0)	5 (9.8)	
	3	1 (0.4)	0 (0)	
	4	0 (0)	0 (0)	
	5	1 (0.4)	0 (0)	
Total		278 (84.5)	51 (15.5)	

Values are presented as number (%).
CL/P, cleft lip with or without cleft palate.
†Chi-square test was performed.
***$P < 0.001$.

formation including chronic disease, medication intake, smoking, alcohol consumption, and exposure to harmful substances (Appendix 1).

All responses were anonymized, and the study protocol was reviewed and approved by the Institutional Review Boards of SNUDH (ERI23014) and KNUDH (KNUDH-2023-01-02-00). Written informed consent was obtained from all participants.

Statistical analysis

Chi-square and Fisher's exact tests were performed using SPSS (version 27; IBM Corp., Armonk, NY, USA). Odds ratio (OR) and 95% confidence interval (CI) were calculated to estimate the magnitudes of association. Statistical significance was set up at $P < 0.05$.

RESULTS

Demographic data of the participants

The body weight at birth and the number of previous births did not differ significantly between the CL/P and non-CL/P groups (all, $P > 0.05$). Although the gestational duration differed between the two groups ($P < 0.001$), a normal gestational duration (≥ 37 weeks) was most commonly observed (93.2% in the CL/P group and 76.5% in the non-CL/P group). Furthermore, the percentage of patients with CL/P who were born early, was low (< 32 weeks, 0.7%) (Table 2).

Demographic data of the parents

The most prevalent ages of mothers at childbirth were 20–29 years and 30–39 years in the CL/P group (50.7% and 47.5%, respectively) and 30–39 years in the non-CL/P group (76.5%). Despite the difference in maternal age between the two groups ($P < 0.001$), the percentages of mothers aged < 19 and > 40 years were low in the CL/P group (1.1% and 0.7%, respectively). In contrast, the father's age at childbirth did not differ between the two groups ($P > 0.05$). The most prevalent father's age was 30–39 years in both the CL/P and non-CL/P groups (75.2% and 82.4%, respectively). The percentages of fathers aged < 19 and > 40 years in the CL/P group were 0% and 6.5%, respectively.

Mother's occupation differed significantly between the two groups ($P < 0.05$), but father's occupations did not ($P > 0.05$). The most common occupations of mothers were housework and office job in the CL/P (49.6% and 40.6%, respectively) and the non-CL/P group (37.3% and 39.2%, respectively). The predominant occupation of fathers in the CL/P and non-CL/P groups was office

job (72.7% and 78.4%, respectively). Similar percentages were observed for physical labor in parents in the CL/P and non-CL/P groups (mothers, 2.2% and 5.9%, respectively; fathers, 10.4% and 11.8%, respectively) (Table 3).

Environmental exposure in the father

The frequencies of chronic diseases, alcohol consumption, and exposure to harmful substances did not differ significantly between the two groups (all, $P > 0.05$). Although the majority of fathers in the CL/P and non-CL/P groups reported no history of chronic disease (86.0% and 88.2%, respectively) or exposure to harmful substances (97.5% and 98.0%, respectively), the alcohol consumption was similar between groups (73.7% and 72.5%, respectively). However, paternal smoking during the periconceptional period was significantly higher in the CL/P group than in the non-CL/P group (61.2% vs. 39.2%; $P < 0.01$; OR = 2.44; 95% CI, 1.32–4.50) (Table 4).

Environmental exposure in the mother

The frequencies of chronic diseases, smoking, secondhand smoking, alcohol consumption, and exposure to harmful substances did not differ significantly between the two groups (all, $P > 0.05$). In the CL/P group and Non-CL/P group, most mothers reported that they did not have chronic diseases (95.3% and 98.0%, respectively), did not smoke (98.6% and 98.0%, respectively), did not experience secondhand smoking (69.4% and 76.5%, respectively), did not drink alcohol (85.6% and 80.4%, respectively), and were not exposed to harmful substances (95.0% and 96.1%, respectively). Medication intake during pregnancy was higher in the CL/P group than in the non-CL/P group (16.2% vs. 3.9%, $P < 0.05$; OR = 4.73; 95% CI, 1.11-20.20), although the exact kinds of medication were not specified.

The frequencies of vitamin and calcium supplementation during pregnancy did not differ significantly between the two groups (all, $P > 0.05$). Most mothers in the CL/P group and non-CL/P groups did not take vitamins (85.6% and 78.4%, respectively) or calcium (68.3% and 72.5%, respectively) during pregnancy. However, folic acid supplementation intake during pregnancy was significantly lower in the CL/P group than in the non-CL/P group (20.9% vs. 68.6%; $P < 0.001$; OR = 0.121; 95% CI, 0.06-0.23) (Table 4).

DISCUSSION

In this study, we aimed to determine which types of environment exposure during pregnancy are risk and protective factors for CL/P.

Demographic data of the participants

Although Kim et al.[1] reported that birth defects are associated with low birth weight, preterm birth, and multiple births, the present study found no association between these factors and CL/P. Most patients with CL/P were born at normal gestational duration, with normal body weight, and as either the first or second child in the family. These findings suggest that the birth conditions of patients with CL/P might differ from those with other congenital birth defects in the heart, blood vessels and kidneys (Table 2).

Table 3. Demographic data of the parents

		Mother			Father		
		CL/P group	Non-CL/P group	*P* value	CL/P group	Non-CL/P group	*P* value
Age at birth (yr)	≤ 19	3 (1.1)	0 (0)	< 0.001***,†	0 (0)	0 (0)	0.148†
	20–29	141 (50.7)	10 (19.6)		51 (18.3)	4 (7.8)	
	30–39	132 (47.5)	39 (76.5)		209 (75.2)	42 (82.4)	
	≥ 40	2 (0.7)	2 (3.9)		18 (6.5)	5 (9.8)	
Occupation	None	0 (0)	0 (0)	0.038*,†	6 (2.2)	0 (0)	0.068†
	Office job	113 (40.6)	20 (39.2)		202 (72.7)	40 (78.4)	
	Physical labor	6 (2.2)	3 (5.9)		29 (10.4)	6 (11.8)	
	House work	138 (49.6)	19 (37.3)		3 (1.1)	0 (0)	
	Others	21 (7.6)	9 (17.6)		35 (12.6)	2 (3.9)	
Total		278 (84.5)	51 (15.5)		278 (84.5)	51 (15.5)	

Values are presented as number (%).
CL/P, cleft lip with or without cleft palate.
†Fisher exact test was performed.
*$P < 0.05$, ***$P < 0.001$.

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Table 4. Environmental exposure in parents

		Mother					Father				
		CL/P group	Non-CL/P group	*P* value	Odd ratio	95% confidence interval	CL/P group	Non-CL/P group	*P* value	Odd ratio	95% confidence interval
Chronic diseases	Yes	12 (4.3)	0 (0)	0.132†,‡	-	-	39 (14.0)	6 (11.8)	0.665‡	-	-
	No	265 (95.3)	50 (98.0)				239 (86.0)	45 (88.2)			
	Treated	1 (0.4)	1 (2.0)				0 (0)	0 (0)			
Medication drug intake	Yes	45 (16.2)	2 (3.9)	0.0170*,†	4.73	1.11–20.20	-	-	-	-	-
	No	233 (83.8)	49 (96.1)				-	-	-	-	-
Smoking	Yes	4 (1.4)	1 (2.0)	0.572†	-	-	170 (61.2)	20 (39.2)	0.004**,‡	2.44	1.32–4.50
	No	274 (98.6)	50 (98.0)				108 (38.8)	31 (60.8)			
Secondhand smoking	Yes	85 (30.6)	12 (23.5)	0.310‡	-	-	-	-	-	-	-
	No	193 (69.4)	39 (76.5)				-	-			
Alcohol consumption	Yes	40 (14.4)	10 (19.6)	0.340‡	-	-	205 (73.7)	37 (72.5)	0.859‡	-	-
	No	238 (85.6)	41 (80.4)				73 (26.3)	14 (27.5)			
Exposure to harmful substances	Yes	14 (5.0)	2 (3.9)	1.000†	-	-	7 (2.5)	1 (2.0)	1.000†	-	-
	No	264 (95.0)	49 (96.1)				271 (97.5)	50 (98.0)			
Vitamin intake	Yes	40 (14.4)	11 (21.6)	0.193‡	-	-	-	-	-	-	-
	No	238 (85.6)	40 (78.4)				-	-			
Folic acid intake	Yes	58 (20.9)	35 (68.6)	< 0.001***,‡	0.121	0.06–0.23	-	-	-	-	-
	No	220 (79.1)	16 (31.4)				-	-			
Calcium intake	Yes	88 (31.7)	14 (27.5)	0.551‡	-	-	-	-	-	-	-
	No	190 (68.3)	37 (72.5)				-	-			

Values are presented as number (%).
CL/P, cleft lip with or without cleft palate.
†Fisher exact test was performed.
‡Chi-square test was performed.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Demographic data of the parents

Savitz et al.[11] reported that old age of the father was associated with a higher risk of cleft palate. However, the present study showed that neither being too young (≤ 19 years) nor too old (≥ 40 years) were significantly associated with the occurrence of CL/P, suggesting that being too young or old may not be a significant risk factor for CL/P. Oldereid et al.[12] also found no significant association between old age of the parents (> 45 years) and orofacial defects. Similar percentages were observed for physical labor in parents in the CL/P and non-CL/P groups suggesting that it also might not be a significant risk factor for CL/P (Table 3).

Environmental exposure in the father

The finding that fathers did not exhibit significant differences in the history of chronic diseases, alcohol consumption, or exposure to harmful substances between the two groups suggests that these attributes might not have meaningful associations with CL/P.

In the present study, fathers' smoking during the periconceptional period appeared to be a significant risk factor for CL/P (OR = 2.44; 95% CI, 1.32–4.50), which was similar to Savitz et al.[11] and Oldereid et al.[12] These findings emphasize the importance of smoking cessation interventions targeting fathers during this critical period (Table 4).

Environmental exposure in the mother

Most mothers did not report chronic diseases (95.3% in the CL/P group and 98.0% in the non-CL/P group, $P > 0.05$). However, the number of mothers with chronic diseases was too low to draw definitive conclusions in the two groups. Balsells et al.[13] and Zhao et al.[14] showed associations between maternal diabetes mellitus and congenital anomalies. Therefore, further studies are necessary to confirm the association between CL/P and chronic diseases in mothers.

In a systematic review and meta-analysis, Lee et al.[6] showed that the association between maternal alcohol consumption during pregnancy and congenital malformations was not significant. Bell et al.[15] also reported no significant association between orofacial clefts and maternal alcohol consumption. These results are similar to those of the current study.

The present study found no association between CL/P and maternal or secondhand smoking. Zheng et al.[16] reported a significant association between oral clefts and secondhand smoking, but not with direct smoking. Differences between the roles of smoking and secondhand smoking in mothers in CL/P occurrence are challenging to understand. This inconsistency highlights the need for further research to clarify the mechanisms by which smoking and secondhand smoking in mothers contribute to the occurrence of CL/P.

Because alcohol consumption and smoking in pregnant women are considered societal taboos, the mothers' alcohol consumption and smoking may have been underreported, and the mothers' secondhand smoking may have been overreported.[16] Therefore, the possibility of under- or over-reporting should be cautiously considered when interpreting these results.

Medication intake by mothers during pregnancy is considered a potential risk factor for various congenital malformations. Previous studies have reported a positive association between maternal valproic acid intake and CL/P and between maternal β-blocker intake and CL/P.[17-19] In the present study, precise drug identification was challenging despite efforts to collect detailed medication information. However, mothers' drug intake during pregnancy appeared to be a significant risk factor for CL/P. Leveraging resources from the National Health Insurance Service in Korea may enable future studies to identify specific drugs associated with CL/P risk.

While Munger et al.[20] reported that vitamin B_{12} serves as a prevention factor for CL/P, the present study found no significant effect of vitamin intake on the prevention of CL/P. However, our findings are consistent with those of Hwang et al.[21] Therefore, further studies are required to verify the relationship between CL/P prevention and multivitamins containing folic acid, with cautious interpretation of the results.

Folic acid intake during the periconceptional period seems to reduce the risk of CL/P.[22-24] This study, revealed a significant protective effect of folic acid intake during pregnancy against CL/P. Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme involved in folate metabolism. van Rooij et al.[24] demonstrated that mothers with the MTHFR 677TT genotype, who did not take folic acid supplements periconceptionally, had a higher risk of producing a baby with CL/P. This may explain the gene-environment interaction in terms of the protective role of folic acid in CL/P.

This study had the following strengths: (1) to our knowledge it is the first comprehensive analysis of the demographic and environmental exposure data in Korean patients with CL/P and their parents; (2) although the number of non-CL/P participants was relatively low, it could be used as a basic reference to obtain the ORs of CL/P prevalence; (3) because orthodontists are actively involved in the diagnosis and treatment of CL/P from birth to completion of facial growth, long-term relationships with patients with CL/P and their parents make it possible to obtain high response rates and collect reliable data.

Although this study provides meaningful insights into the public health interventions aimed at reducing the incidence of CL/P, the findings should be interpreted with

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caution. The limitations of the present study are: (1) the retrospective nature of the study design, (2) the small sample size of non-CLP patients, (3) the methodology of the retrospective survey that relied on experiences and memories of parents, and (4) that parts of some of the questionnaires were not completed. Therefore, further studies with a prospective design, larger sample size, the inclusion of parents who can remember clearly, and more sophisticated statistical analysis, should be performed (Table 4).

CONCLUSIONS

Although this study provides basic information explaining the association between environmental factors and CL/P risk, further studies are necessary to confirm the findings and explore their clinical implications.

AUTHOR CONTRIBUTIONS

Conceptualization: MH, SHB. Data curation: MJK, NPL, HH, JWP, MH, SHB. Formal analysis: NPL, MH, SHB. Methodology: MJK, NPL, HSP, JWP, MH, SHB. Project administration: MH, SHB. Resources: HH, HSP, MMT, IHY, MH, SHB. Supervision: MH, SHB. Writing–original draft: MJK, MH, SHB. Writing–review & editing: All authors.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Kim MA, Yee NH, Choi JS, Choi JY, Seo K. Prevalence of birth defects in Korean livebirths, 2005-2006. J Korean Med Sci 2012;27:1233-40. https://doi.org/10.3346/jkms.2012.27.10.1233
2. Kim S, Kim WJ, Oh C, Kim JC. Cleft lip and palate incidence among the live births in the Republic of Korea. J Korean Med Sci 2002;17:49-52. https://doi.org/10.3346/jkms.2002.17.1.49
3. Hong M, Baek SH. Trend of health care utilization of cleft lip and/or palate in Korea during 2007-2016. Korean J Orthod 2018;48:216-23. https://doi.org/10.4041/kjod.2018.48.4.216
4. Baek SH, Moon HS, Yang WS. Cleft type and Angle's classification of malocclusion in Korean cleft patients. Eur J Orthod 2002;24:647-53. https://doi.org/10.1093/ejo/24.6.647
5. Park HM, Kim PJ, Kim HG, Kim S, Baek SH. Prediction of the need for orthognathic surgery in patients with cleft lip and/or palate. J Craniofac Surg 2015;26:1159-62. https://doi.org/10.1097/scs.0000000000001605
6. Lee KS, Choi YJ, Cho J, Lee H, Lee H, Park SJ, et al. Environmental and genetic risk factors of congenital anomalies: an umbrella review of systematic reviews and meta-analyses. J Korean Med Sci 2021;36:e183. https://doi.org/10.3346/jkms.2021.36.e183
7. Kang G, Baek SH, Kim YH, Kim DH, Park JW. Genetic risk assessment of nonsyndromic cleft lip with or without cleft palate by linking genetic networks and deep learning models. Int J Mol Sci 2023;24:4557. https://doi.org/10.3390/ijms24054557
8. Jayarajan R, Natarajan A, Nagamuttu R. Efficacy of periconceptional high-dose folic acid in isolated orofacial cleft prevention: a systematic review. Indian J Plast Surg 2019;52:153-9. https://doi.org/10.1055/s-0039-1696864
9. Chowchuen B, Surakunprapha P, Winaikosol K, Punyavong P, Kiatchoosakun P, Pradubwong S. Birth prevalence and risk factors associated with CL/P in Thailand. Cleft Palate Craniofac J 2021;58:557-66. https://doi.org/10.1177/1055665620956896
10. Silvestre CMR, Silva AMC, Ferreira da Silva RCG, Bittencourt WS, Borba AM, Fernandes V, et al. Environmental factors at the periconceptional period and the occurrence of cleft lip and palate in a midwest brazil population: a case-control study. J Occup Environ Med 2022;64:e751-6. https://doi.org/10.1097/jom.0000000000002689
11. Savitz DA, Schwingl PJ, Keels MA. Influence of paternal age, smoking, and alcohol consumption on congenital anomalies. Teratology 1991;44:429-40. https://doi.org/10.1002/tera.1420440409
12. Oldereid NB, Wennerholm UB, Pinborg A, Loft A, Laivuori H, Petzold M, et al. The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis. Hum Reprod Update 2018;24:320-89. https://doi.org/10.1093/humupd/dmy005
13. Balsells M, García-Patterson A, Gich I, Corcoy R. Major congenital malformations in women with gestational diabetes mellitus: a systematic review and meta-analysis. Diabetes Metab Res Rev 2012;28:252-7. https://doi.org/10.1002/dmrr.1304
14. Zhao E, Zhang Y, Zeng X, Liu B. Association between maternal diabetes mellitus and the risk of congenital malformations: a meta-analysis of cohort studies. Drug Discov Ther 2015;9:274-81. https://doi.org/10.5582/ddt.2015.01044
15. Bell JC, Raynes-Greenow C, Turner RM, Bower C,

Nassar N, O'Leary CM. Maternal alcohol consumption during pregnancy and the risk of orofacial clefts in infants: a systematic review and meta-analysis. Paediatr Perinat Epidemiol 2014;28:322-32. https://doi.org/10.1111/ppe.12131
16. Zheng Z, Xie G, Yang T, Qin J. Congenital malformations are associated with secondhand smoke among nonsmoking women: a meta-analysis. Birth 2019;46:222-33. https://doi.org/10.1111/birt.12401
17. Yakoob MY, Bateman BT, Ho E, Hernandez-Diaz S, Franklin JM, Goodman JE, et al. The risk of congenital malformations associated with exposure to β-blockers early in pregnancy: a meta-analysis. Hypertension 2013;62:375-81. https://doi.org/10.1161/hypertensionaha.111.00833
18. Tanoshima M, Kobayashi T, Tanoshima R, Beyene J, Koren G, Ito S. Risks of congenital malformations in offspring exposed to valproic acid in utero: a systematic review and cumulative meta-analysis. Clin Pharmacol Ther 2015;98:417-41. https://doi.org/10.1002/cpt.158
19. Davenport MH, Yoo C, Mottola MF, Poitras VJ, Jaramillo Garcia A, Gray CE, et al. Effects of prenatal exercise on incidence of congenital anomalies and hyperthermia: a systematic review and meta-analysis. Br J Sports Med 2019;53:116-23. https://doi.org/10.1136/bjsports-2018-099653
20. Munger RG, Kuppuswamy R, Murthy J, Balakrishnan K, Thangavel G, Sambandam S, et al. Maternal vitamin B_{12} status and risk of cleft lip and cleft palate birth defects in Tamil Nadu State, India. Cleft Palate Craniofac J 2021;58:567-76. https://doi.org/10.1177/1055665621998394
21. Hwang SJ, Beaty TH, Panny SR, Street NA, Joseph JM, Gordon S, et al. Association study of transforming growth factor alpha (TGF alpha) TaqI polymorphism and oral clefts: indication of gene-environment interaction in a population-based sample of infants with birth defects. Am J Epidemiol 1995;141:629-36. https://doi.org/10.1093/oxfordjournals.aje.a117478
22. Tolarova M. Periconceptional supplementation with vitamins and folic acid to prevent recurrence of cleft lip. Lancet 1982;2:217. https://doi.org/10.1016/s0140-6736(82)91063-7
23. Shaw GM, Lammer EJ, Wasserman CR, O'Malley CD, Tolarova MM. Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. Lancet 1995;346:393-6. https://doi.org/10.1016/s0140-6736(95)92778-6
24. van Rooij IA, Vermeij-Keers C, Kluijtmans LA, Ocké MC, Zielhuis GA, Goorhuis-Brouwer SM, et al. Does the interaction between maternal folate intake and the methylenetetrahydrofolate reductase polymorphisms affect the risk of cleft lip with or without cleft palate? Am J Epidemiol 2003;157:583-91. https://doi.org/10.1093/aje/kwg005

Appendix 1. Cleft survey questionnaire used in the present study

CLP survey

Clinic site: KNUDH
Examiner: _____
Date of exam: ___ ___ 2023
MM DD YYYY
Chart number: _____

Patient

Name			Birth date			
Sex	M F		Prior parity		_____	
Birth weight	_____ kg	< 2.4 kg	2.5–2.9 kg	2.9–3.7 kg	3.7–4.1 kg	Over 4.2 kg
Gestational age	_____ wk		< 32 wk		33–36 wk	Over 37 wk
Diagnosis	Cleft palate		Cleft lip with/without cleft alveolus		Cleft lip and palate	
Diagnosis (Specified)	Cleft palate		Unilateral cleft lip	Unilateral cleft lip with cleft alveolus	Unilateral CLP	
			Bilateral cleft lip	Bilateral cleft lip with cleft alveolus	Bilateral CLP	
Accompanied syndrome	N Y		Syndrome type:			

Mother

Name			Birth date			
Age at birth	_____		< 19 yr	20–29 yr	30–39 yr	Over 40 yr
Occupation	Office job		Physical labor		Housework	etc.
Education	Under middle school		High school		College graduate	

Father

Name			Birth date			
Age at birth	_____		< 19 yr	20–29 yr	30–39 yr	Over 40 yr
Occupation	Office job		Physical labor		Housework	etc.
Education	Under middle school		High school		College graduate	

Monthly income	< ₩2,000,000	< ₩2,000,000–4,000,000	Over ₩4,000,000

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 https://doi.org/10.4041/kjod24.137

Family history

CLP family history	Y N

Immediate family

	Father	Mother	Brother	Sister
Type	Cleft palate	Cleft lip/alveolus	Cleft lip and palate	Unknown

	Grandfather	Grandmother	Uncle/aunt	Cousin	Other relatives
Type	Cleft palate	Cleft lip/alveolus	Cleft lip and palate	Unknown	

Father's information

* Draw a horizontal line

Smoking during pregnancy		No Yes	
	Pregestation (−3 to −1 mo)	First stages (1−3 mo)	Second trimester~ (4−9 mo)
Duration			

Alcohol drinking	No Yes Quit (When _____)
Alcohol consumption	1−3/mo, 1−3/wk, over 4 time/wk

Chronic diseases	No Yes Treated				
	DM	HT	Cardiovascular diseases	Epilepsy	Cancer
	Psychopathy	Bleeding disorders	Autoimmune diseases	Infectious diseases	etc.
Disease	Age	Illness during pregnancy	Duration (during pregnancy)	Therapy method	Medication
		No Yes	mo − mo		
		No Yes	mo − mo		
		No Yes	mo − mo		

* Draw a horizontal line

Exposure of harmful substances (chemicals, radioactivity, pesticides, etc.)		No Yes	
	Pregestation (−3 to −1 mo)	First stages (1−3 mo)	Second trimester~ (4−9 mo)
Exposed time			

https://doi.org/10.4041/kjod24.137

Mother's information

* Draw a horizontal line

Drug history		Pregestation (−3 to −1 mo)	First stages (1−3 mo)	Second trimester~ (4−9 mo)
Vitamin	No Yes			
Folic acid	No Yes			
Calcium	No Yes			
Antibiotics	No Yes			
Steroid	No Yes			
etc.	No Yes			

Smoking		No Yes Quit (When _____)	
	Pregestation (−3 to −1 mo)	First stages (1−3 mo)	Second trimester~ (4−9 mo)
Duration			

Secondhand smoking		No Yes	
	Pregestation (−3 to −1 mo)	First stages (1−3 mo)	Second trimester~ (4−9 mo)
Duration			

Alcohol drinking: No Yes Quit (When _____)	Alcohol consumption: 1−3/mo, 1−3/wk, over 4 time/wk		
	Pregestation (−3 to −1 mo)	First stages (1−3 mo)	Second trimester~ (4−9 mo)
Duration			

Chronic diseases	No Yes Treated				
	DM	HT	Cardiovascular disease	Epilepsy	Cancer
	Psychopathy	Bleeding disorder	Autoimmune disease	Infectious disease	etc.
Disease	Age	Illness during pregnancy	Duration (during pregnancy)	Therapy method	Medication
		No Yes	mo − mo		
		No Yes	mo − mo		
		No Yes	mo − mo		

Exposure of harmful substances (chemicals, radioactivity, pesticides, etc.)		No Yes	
	Pregestation (−3 to −1 mo)	First stages (1−3 mo)	Second trimester~ (4−9 mo)
Exposed time			

 https://doi.org/10.4041/kjod24.137