

Prevalence of orofacial clefts in Korean live births

Chung Won Lee, Sun Mi Hwang, You Sun Lee, Min-A Kim, Kyung Seo

Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Institute of Women's Medical Life Science, Yonsei University College of Medicine, Seoul, Korea

Objective

The aim of this study was to investigate the prevalence of orofacial clefts and identify the characteristics of other birth defects associated with orofacial clefts in Korea.

Methods

This study used data from the Congenital Anomaly Survey conducted by the Korea Institute for Health and Social Affairs. The survey was conducted on birth defects documented during 2005 to 2006 in 2,348 medical institutes in Korea. This study was performed using data from medical insurance claims of the National Health Insurance Corporation. The prevalence of orofacial clefts was defined as the number of cases per 10,000 live births.

Results

Among the 883,184 live births, 25,335 infants had birth defects, which included 980 infants with orofacial clefts. The prevalence of total orofacial clefts in the total live births was 11.09 per 10,000, accounting for 3.9% of all birth defects. The most common orofacial cleft was cleft palate only ($n=492$), followed by cleft lip only ($n=245$) and cleft lip with cleft palate ($n=243$), with prevalence rates of 5.57, 2.77, 2.75 per 10,000 live births, respectively. While malformations of the circulatory system; digestive system; eyes, ears, face, and neck; and musculoskeletal system were most frequently encountered among infants with a cleft lip with or without a cleft palate, anomalies of most organ systems were notably observed among infants with cleft palate only.

Conclusion

The prevalence of orofacial clefts in Korea was similar or slightly lower than that of other countries. This study informs present status of orofacial clefts and gives baseline data to lay the foundation stone for Korea's registry system of orofacial clefts.

Keywords: Cleft lip; Cleft palate; Korea; Orofacial clefts; Prevalence

Introduction

Birth defects not only lead to infant mortality, childhood morbidity, and mortality but also entail large amounts of medical expenditures. Orofacial clefts are one of the most common birth defects [1]. In general, the types of orofacial clefts are classified into a cleft lip either with or without a cleft palate (CL \pm P) or a cleft palate only (CPO). The phenotypes of these defects are thought to be caused by distinct etiologies, based on many genetic and environmental factors [2,3]. Although no definite relationship between orofacial clefts and other birth defects has been shown, several studies have reported that orofacial clefts are associated with congenital malformations [4].

The prevalence of orofacial clefts varies between and within countries. The estimated incidence of orofacial clefts worldwide is approximately 10 to 22.1 per 10,000 live births [5].

According to Canfield et al. [1], the estimated incidence of cleft lip with cleft palate (CLP) in the United States was 10.5 per 10,000 live births and that of CPO was 6.4 per 10,000 live births. A wide range of CLP prevalence, from 2.7 per 10,000 births in Spain to 20.2 per 10,000 births in Japan, was

Received: 2014.8.27. Revised: 2014.10.12. Accepted: 2014.10.16.

Corresponding author: Kyung Seo

Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 135-720, Korea

Tel: +82-2-2019-3433 Fax: +82-2-3462-8209

E-mail: kyungseo@yuhs.ac

Articles published in *Obstet Gynecol Sci* are open-access, distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2015 Korean Society of Obstetrics and Gynecology

reported by the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) in 2009 [6].

Although the prevalence of orofacial clefts differs between countries and races, the epidemiology of orofacial clefts in Korea has not been investigated widely. The purpose of this study was to investigate the prevalence of orofacial clefts in a Korean live birth population and examine the occurrence pattern with other birth defects in infants with orofacial clefts.

Materials and methods

In this study, we analyzed congenital anomaly data in live births between 2005 and 2006 that were collected from a survey conducted by the Korea Institute for Health and Social Affairs. The data were based on the medical insurance claims of the National Health Insurance Corporation in the entire Republic of Korea. The study categories and subjects were chosen earlier, and for effective data selection, data were collected using a Web-based research system. Real-time monitoring of the progress status was conducted during the research period in order to promptly respond to demands and issues raised through the research web site. Considering possible weak points, the data collected were reviewed and analyzed for variations or duplications in diagnoses between medical institutions. Owing to the different times of diagnosis of the birth defects, depending on the type of disease, the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) and the European Surveillance of Congenital Anomalies (EUROCAT) have been updating statistical data, including the diagnoses 1 year after birth. Likewise, our study included diagnoses at the first postnatal year. The Korean Medical Record Association evaluates the progress of research and directly gathers data from birth defect databases.

Birth defects were classified according to the organ system primarily affected and the individual disease subtype, according to the 10th Revision of the International Classification of Diseases, and they were examined according to groups of birth defects managed by EUROCAT, ICBDSR, and the National Birth Defects Prevention Network, which perform title roles globally in this field.

In this study, we examined the medical insurance claims database containing data on birth defects during the first postnatal year (referring to the main disease code and sub-code) to collect subject information and explore risk factors of birth defects that might be determined from the medical records. All sub-

jects with the 5th Korean Standard Classification of Diseases, Q code, which indicates a congenital anomaly, were selected. Orofacial anomalies were divided into CPO (Q35), cleft lip only (CLO, Q36), and CLP (Q37).

Analysis was performed for 38,396 subjects from 2,505 medical institutions all over Korea. By organizing results according to the affiliated medical institution, 38,199 subjects were selected from 2,348 medical institutions, which consisted of 250 general hospitals, 260 hospitals, 1830 clinics, 7 public health centers, and 1 oriental medicine health organization. Above all, for each patient, data pertaining to the same disease were collected from different institutions and sorted for review. After reconfirming the diagnosis in each subject, 32,727 study subjects were diagnosed with or suspected to have at least one birth defect. Patients with suspected diagnoses of birth defects and minor anomalies diagnosed in local outpatient clinics or duplicated cases were excluded. Eventually, for the analysis, 25,335 study subjects were selected among infants born between 2005 and 2006.

We analyzed the live birth prevalence of orofacial clefts by dividing the number of live births with orofacial clefts by the total number of live births, and expressed the prevalence of orofacial clefts per 10,000 live births.

Results

Between 2005 and 2006, 883,184 infants were born alive, with 435,031 in 2005 and 448,153 in 2006. Of these total live births, 25,335 infants were born with birth defects, among whom 980 had orofacial cleft defects. Thus, the prevalence of orofacial clefts was 11.09 per 10,000 live births, accounting for 3.9% of all birth defects. CPO was the most frequent type, with a prevalence of 5.57 per 10,000 live births, accounting for 50.2% of all orofacial clefts, followed by CLO at a prevalence of 2.77 per 10,000 live births (25%) and CLP at a prevalence of 2.75 per 10,000 live births (24.8%). The prevalence of orofacial clefts in live birth infants is shown in Table 1.

Among the 980 infants with a cleft, 481 (49.1%) were male infants and 499 (51.0%) were female infants. CL±P was more frequent in male infants, as indicated by the male-to-female ratios of 1.64 among the CLP cases and 1.43 among the CLO cases. Meanwhile, CPO was more frequent in female infants (n=306) than in male infants (n=186) based on the fetal sex ratio of 0.61. The distribution of the orofacial cleft subjects according to fetal sex, multiple birth, maternal age, gestational

age, and cleft phenotype is presented in Table 2.

Of the 980 infants with a cleft, 531 had other birth defects, accounting for 45.8% of orofacial clefts. This means that approximately half of the children born with orofacial clefts had other birth defects. In the pool of infants with birth defects, circulatory system anomalies were the most related with orofacial cleft defects, accounting for 12.8% of live births with orofacial

facial clefts, followed by digestive and musculoskeletal system anomalies at prevalence rates of 6.7% and 5.7%, respectively (Table 3). In the circulatory system, atrial septal defects (ASDs) were the most common orofacial cleft birth defect, occurring in 75 orofacial cleft subjects (7.7%), with 9.3% having CPO, 9.1% having CLP, and 2.9% having CLO. The next most common birth defect of the circulatory system was ventricular

Table 1. Prevalence of orofacial clefts in Korea

| | Total number of cases | Proportion in orofacial clefts (%) | Prevalence per 10,000 total live births | 95% confidence interval |
|--------------------------|-----------------------|------------------------------------|---|-------------------------|
| Cleft lip without palate | 245 | 25.0 | 2.77 | 2.43–3.12 |
| Cleft lip with palate | 243 | 24.8 | 2.75 | 2.41–3.10 |
| Cleft palate only | 492 | 50.2 | 5.57 | 5.08–6.06 |
| Total | 980 | 100.0 | 11.09 | 10.40–11.79 |

Table 2. Demographic characteristics according to orofacial cleft type

| | Total | Cleft lip without palate | Cleft lip with palate | Cleft palate only |
|-------------------------------|---------------|--------------------------|-----------------------|-------------------|
| Maternal age (yr) | 30.5±4.2 | 30.5±4.2 | 30.7±4.8 | 30.4±3.9 |
| Gestational age (wk) | 38.6±2.3 | 38.5±2.6 | 38.5±2.3 | 38.7±2.1 |
| Birth weight (g) | 3,098.4±579.0 | 3,110.4±601.8 | 3,088.6±594.3 | 3,097.2±561.4 |
| Fetal sex ratio (male/female) | 0.96 | 1.43 | 1.64 | 0.61 |
| Multiple births (%) | 2.8 | 3.3 | 3.7 | 2.0 |

Table 3. Association of orofacial clefts with other congenital anomalies in Korea, 2005 to 2006

| Birth defects (ICD-10) | Total (n=980) | Cleft lip without palate (n=245) | Cleft lip with palate (n=243) | Cleft palate only (n=492) |
|--|---------------|----------------------------------|-------------------------------|---------------------------|
| Isolated clefts | 531 (54.2) | 192 (78.4) | 145 (59.7) | 194 (39.4) |
| Other birth defects associated with orofacial clefts | 449 (45.8) | 53 (21.6) | 98 (40.3) | 298 (60.6) |
| Nervous system (Q00–07) | 20 (2.0) | 1 (0.4) | 7 (2.9) | 12 (2.4) |
| Eye, ear, face, and neck (Q10–18) | 49 (5.0) | 7 (2.9) | 13 (5.3) | 29 (5.9) |
| Circulatory system (Q20–28) | 125 (12.8) | 14 (5.7) | 30 (12.3) | 81 (16.5) |
| Respiratory system (Q30–34) | 17 (1.7) | 4 (1.6) | 1 (0.4) | 12 (2.4) |
| Digestive system (Q38–45) | 66 (6.7) | 13 (5.3) | 14 (5.8) | 39 (7.9) |
| Genital organs (Q50–56) | 19 (1.9) | 2 (0.8) | 3 (1.2) | 14 (2.8) |
| Urinary system (Q60–64) | 21 (2.1) | 3 (1.2) | 6 (2.5) | 12 (2.4) |
| Musculoskeletal system (Q65–79) | 56 (5.7) | 6 (2.4) | 11 (4.5) | 39 (7.9) |
| Other and unspecified (Q80–89) | 45 (4.6) | 3 (1.2) | 6 (2.5) | 36 (7.3) |
| Chromosomal abnormalities (Q90–99) | 31 (3.2) | 0 (0) | 7 (2.9) | 24 (4.9) |

ICD-10, the tenth revision of the International Classification of Diseases.

Table 4. Prevalence and distribution of individual malformation recorded

| Birth defects (ICD-10) | Total (n=980) | Cleft lip without palate (n=245) | Cleft lip with palate (n=243) | Cleft palate only (n=492) |
|---|---------------|----------------------------------|-------------------------------|---------------------------|
| Nervous system (Q00–07) | | | | |
| Encephalocele (Q01.0–01.9) | 1 (0.1) | 0 (0) | 1 (0.4) | 0 (0) |
| Microcephaly (Q02) | 5 (0.5) | 0 (0) | 2 (0.8) | 3 (0.6) |
| Congenital Hydrocephalus (Q03.0–03.9) | 5 (0.5) | 1 (0.4) | 1 (0.4) | 3 (0.6) |
| Holoprosencephaly (Q04.0–04.2) | 9 (0.9) | 0 (0) | 4 (1.6) | 5 (1.0) |
| Spina bifida (Q05.0–05.9) | 2 (0.2) | 0 (0) | 0 (0) | 2 (0.4) |
| Eye, ear, face, and neck (Q10–18) | | | | |
| Microphthalmos (Q11.2) | 3 (0.3) | 1 (0.4) | 1 (0.4) | 1 (0.2) |
| Congenital cataract (Q12.0) | 1 (0.1) | 0 (0) | 0 (0) | 1 (0.2) |
| Aniridia (Q13.1) | 1 (0.1) | 1 (0.4) | 0 (0) | 0 (0) |
| Congenital glaucoma (Q15.0) | 1 (0.1) | 0 (0) | 0 (0) | 1 (0.2) |
| Microtia (Q17.2) | 11 (1.1) | 0 (0) | 9 (1.8) | 2 (0.8) |
| Circulatory system (Q20–28) | | | | |
| Ventricular septal defect (Q21.0) | 31 (3.2) | 3 (1.2) | 8 (3.3) | 20 (4.1) |
| Atrial septal defect (Q21.1) | 75 (7.7) | 7 (2.9) | 22 (9.1) | 46 (9.3) |
| Tetralogy of Fallot (Q21.3) | 9 (0.9) | 1 (0.4) | 2 (0.8) | 6 (1.2) |
| Pulmonary valve atresia/stenosis (Q22.0–22.1) | 3 (0.3) | 0 (0) | 1 (0.4) | 2 (0.4) |
| Patent ductus arteriosus (Q25.0) ^{a)} | 30 (3.1) | 5 (2.0) | 7 (2.9) | 18 (3.7) |
| Coarctation of aorta (Q25.1) | 7 (0.7) | 0 (0) | 1 (0.4) | 6 (1.2) |
| Aortic atresia/stenosis (Q23.0) | 1 (0.1) | 0 (0) | 0 (0) | 1 (0.2) |
| DORV (Q20.1) | 2 (0.2) | 0 (0) | 1 (0.4) | 1 (0.2) |
| AVSD (Q35.8) | 7 (0.7) | 1 (0.4) | 1 (0.4) | 5 (1.0) |
| Respiratory system (Q30–34) | | | | |
| Choanal atresia (Q30.0) | 3 (0.3) | 1 (0.4) | 0 (0) | 2 (0.4) |
| Digestive system (Q38–45) | | | | |
| Esophageal atresia/stenosis (Q39.0–39.1) | 4 (0.4) | 0 (0) | 1 (0.4) | 3 (0.6) |
| Anorectal atresia/stenosis (Q42.0–42.3) | 1 (0.1) | 0 (0) | 1 (0.4) | 0 (0) |
| Genital organs (Q50–56) | | | | |
| Undescended testis (Q53.0–53.9) ^{b)} | 13 (1.3) | 1 (0.4) | 3 (1.2) | 9 (1.8) |
| Hypospadias (Q54.0–54.9) | 5 (0.5) | 0 (0) | 1 (0.4) | 4 (0.8) |
| Indeterminate sex (Q56.0–56.4) | 1 (0.1) | 0 (0) | 0 (0) | 1 (0.2) |
| Urinary system (Q60–64) | | | | |
| Renal agenesis (Q60.0–60.6) | 3 (0.3) | 1 (0.4) | 1 (0.3) | 1 (0.2) |
| Cystic kidney (Q61.0–61.9) | 2 (0.2) | 0 (0) | 1 (0.4) | 1 (0.2) |
| Congenital hydronephrosis (Q62.0) | 14 (1.4) | 2 (0.8) | 4 (1.6) | 8 (1.6) |
| Obstructive genitourinary defect (Q62.0–62.8, Q64.3) | 15 (1.5) | 2 (0.8) | 4 (1.6) | 9 (1.8) |
| Musculoskeletal system (Q65–79) | | | | |
| Congenital hip dislocation (Q65.0–65.9) | 5 (0.5) | 0 (0) | 1 (0.4) | 4 (0.8) |
| Polydactyly (Q69.0–69.9) | 8 (0.8) | 2 (0.8) | 1 (0.4) | 5 (1.0) |
| Syndactyly (Q70.0–70.9) | 9 (0.9) | 1 (0.4) | 2 (0.8) | 6 (1.2) |
| Upper limb reduction defects (Q71.0–Q71.9) | 4 (0.4) | 1 (0.4) | 2 (0.8) | 1 (0.2) |
| Lower limb reduction defects (Q72.0–Q72.9) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Total limb reduction defects (Q71.0–71.9, Q72.0–72.9, Q73.0–73.8) | 4 (0.4) | 1 (0.4) | 2 (0.8) | 1 (0.2) |
| Craniosynostosis (Q75.0) | 2 (0.2) | 0 (0) | 0 (0) | 2 (0.4) |
| Diaphragmatic hernia (Q79.0) | 3 (0.3) | 0 (0) | 1 (0.4) | 2 (0.4) |
| Chromosomal abnormalities (Q90–99) | | | | |
| Trisomy 13 (Q91.4–91.6) | 3 (0.3) | 0 (0) | 2 (0.8) | 1 (0.2) |
| Down syndrome (Q90.0–90.9) | 5 (0.5) | 0 (0) | 1 (0.4) | 4 (0.8) |
| Turner syndrome (Q96.0–96.9) | 1 (0.1) | 0 (0) | 0 (0) | 1 (0.2) |
| Klinefelter syndrome (Q98.0–98.4) | 1 (0.1) | 0 (0) | 0 (0) | 1 (0.2) |
| Wolf-Hirschorn syndrome (Q93.3) | 2 (0.2) | 0 (0) | 2 (0.8) | 0 (0) |
| Cri-du-hat syndrome (Q93.4) | 2 (0.2) | 0 (0) | 0 (0) | 2 (0.4) |

ICD-10, the tenth revision of the International Classification of Diseases; DORV, double outlet right ventricle; AVSD, atrio ventricular septal defects.

^{a)}Patent ductus arteriosus was excluded if birth weight was less than 2,500 g; ^{b)}Undescended testis was excluded if gestational age was less than 36 weeks.

septal defect (VSD), accounting for 3.2%, 4.1%, 3.3%, and 1.2% of the total orofacial cleft, CPO, CLP, and CLO cases, respectively, followed by patent ductus arteriosus (PDA; 3.1%, 3.7%, 2.9%, and 2.0%, respectively) (Table 4). Infants with CPO showed malformations of most organ systems, whereas infants with CL±P notably showed anomalies of the eyes, ears, face, neck, and digestive system. The total number of infants with isolated orofacial clefts was 449, indicating a prevalence of 5.1 per 10,000 live births, whereas that of infants with associated orofacial clefts was 531, rendering a prevalence of 6.0 per 10,000 live births.

The seven major anomalies in the infants with orofacial clefts according to prevalence were ASDs (7.7%), VSDs (3.2%), PDA (3.1%), obstructive genitourinary defects (1.5%), congenital hydronephrosis (1.4%), undescended testis (1.3%), and syndactyly (0.9%) (Table 4). In particular, the incidence rates of ASDs, VSDs, and PDA were higher than those of other defects.

Moreover, in multiple births, the incidence rates of CLP, CLO, and CPO were high at 3.7%, 3.3%, and 2.0%, respectively (Table 2). The distributions of infants with orofacial clefts according to maternal age, gestational age, and birth weight were similar in our study, unlike the prevalence of CLP at birth in the United States, which was higher among mothers aged 25 to 29 years than among mothers aged 30 to 34 years, with a prevalence ratio of 0.8 (95% confidence interval, 0.7 to 0.9) [7]. The most common chromosomal abnormality associated with orofacial clefts was Down syndrome, with a prevalence rate of 0.8% in CPO cases and 0.4% in CLP cases (Table 4).

Discussion

Epidemiological studies have investigated the distribution of orofacial clefts in different countries, territories, and races. However, in Korea, because most studies included subjects from a single institution or district, data on the prevalence of birth defects were not reliable. The prevalence of orofacial clefts among Koreans has not been reported thus far. In our study, the nationwide prevalence and phenotypes of orofacial clefts in Korea were analyzed.

During 2005 to 2006, the prevalence of birth defects in Korea was found to be 286.9 per 10,000 live births. Of the 25,335 subjects, 980 infants had orofacial clefts, indicating a prevalence of 11.09 per 10,000 live births, which is 3.9% of live-born infants with birth defects. Orofacial clefts are most commonly related to other major malformations, and our

study showed that 45.8% of infants with orofacial clefts had other associated birth defects.

The prevalence of orofacial clefts varies across countries. In the United States, the prevalence of CLP was 10.5 per 10,000 live births in 2006, whereas it was 2.7 per 10,000 live births in Spain and 20.2 per 10,000 live births in Japan, based on the ICBDMs in 2009. Among all the orofacial clefts, associated circulatory system anomalies were the most prevalent at 12.8%, followed by digestive system (6.7%), musculoskeletal system (5.7%), and eye, ear, face, and neck anomalies (5.0%). The most common birth defect in Korea was ASD in association with orofacial clefts. Other studies reported various estimates of prevalence of orofacial clefts associated with congenital anomalies, ranging from 3% by Fraser in 1970 [8] to 64.2% by Shaw et al. in 2004 [9]. Several studies have reported that cardiovascular anomalies were the most common malformations related to orofacial cleft defects, while other studies have found head and neck malformations to be the most common associated anomalies [10-15]. This discrepancy may be due to not only the varied subjects based on the population of countries, regions, and races but also the different standards for inclusion and exclusion, which were ascertained differently.

Associated anomalies were most frequent in infants with CPO (n=298, 60.6%), followed by CLP (n=98, 40.3%) and CLO (n=53, 21.6%). Shaw et al. [9] reported that the prevalence of associated congenital anomalies was 71% for subjects with CPO, whereas Milerad et al. [10] noted that 22% of their subjects with CPO had associated anomalies. Consistent with the National Birth Defects Prevention Study data, our study found that CLO and CLP were more prevalent among male infants, whereas CPO was more prevalent among female infants [7]. In the past, the patterns of CPO in both sexes had been similar until many studies showed a higher incidence in girls [5]. The tendency toward increasing prevalence in female infants with CPO should be further studied to determine the changing epidemiology. Meanwhile, male infants were found to be more affected with CLP and CLO, with fetal sex ratios of 1.64 and 1.43, respectively. Although the prevalence of birth defects was higher in male infants than in female infants based on our data, the prevalence of orofacial clefts was higher in female infants than in male infants. In total, 499 female infants had orofacial clefts, consisting of 306 CPO cases, 144 CLO cases, and 92 CLP cases, whereas 481 male infants had orofacial clefts, consisting of 186 CPO cases, 151 CLP cases, and 144 CLO cases.

Among the subjects with CPO, most organ systems were

notably affected. Meanwhile, malformations of the circulatory system; digestive system; eyes, ears, face, and neck; and musculoskeletal system were most common among infants with CL±P. Dividing the CL±P group according to the organ systems affected, the incidence of associated anomalies were more significant in the CLP group than in the CLO group. Likewise, considering chromosomal anomalies, Down syndrome was significantly more prevalent in the CPO group (0.8%) than in the CLP (0.4%) and CLO groups (0%).

In 1958, systematic collection and monitoring of data on birth defects were initiated in Birmingham, United Kingdom [16]. Since then, investigations on birth defects have proliferated worldwide. In particular, the role of ascertaining data on birth defects is performed by EUROCAT for Europe and by the Centers for Disease Control and Prevention for the United States. By contrast, Korea had no such monitoring system. Because a system of monitoring and collection for statistical data has not been established, Korea has not yet strongly functioned to improve the treatment of birth defects and the quality of life of such patients. Considering that birth defects are affected by changes in environmental factors and conditions, global teamwork is needed to develop effective prevention and management.

This study has some limitations because it only analyzed congenital anomaly survey data collected by the Korea Institute for Health and Social Affairs, depending on the diagnosis and reports from 2,348 medical institutes, which might have included possible errors in entering the disease code at diagnosis and excluded unreported cases. Therefore, collecting data from medical records showing initial diagnoses of congenital anomalies without performing reexamination might have resulted in statistical errors regarding the number of subjects. Moreover, medical records might have been prepared differently by the physicians, of whom some might have entered only the main disease code, whereas others might have included the specific sub-code of the disease. In this case, collecting subsidiary information about the disease subjects is recommended to improve study reliability.

In addition, accurate history-taking of the medications administered during pregnancy and the mother's occupation, living condition, and genetic traits is required to better understand the relationship between environmental factors and birth defects, whereas our data did not have comprehensive archives. Thus, further studies are required in the future for a more accurate and reliable investigation.

As birth defects are the constant cause of spontaneous abortions and infant deaths [17], the percentage of birth defects

will increase and so will the prevalence of orofacial clefts. It is possible that the prevalence of orofacial clefts in Korea was underestimated because of pregnancy terminations, stillbirths, and spontaneous abortions. The changing trends of birth defects must be monitored and investigated regularly to prevent and manage birth defects more efficiently. This study was the first large-scale investigation of orofacial clefts in Korea, which aimed to present the recent status and incidence pattern of orofacial clefts in the country. Further study may direct us to understand the factors related to orofacial clefts, support the public health care system in terms of developing preventive measures, and provide better knowledge and instructions to physicians who treat such patients.

Conflict of interest

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

References

1. Canfield MA, Honein MA, Yuskiv N, Xing J, Mai CT, Collins JS, et al. National estimates and race/ethnic-specific variation of selected birth defects in the United States, 1999-2001. *Birth Defects Res A Clin Mol Teratol* 2006;76:747-56.
2. Murray JC. Gene/environment causes of cleft lip and/or palate. *Clin Genet* 2002;61:248-56.
3. Spritz RA. The genetics and epigenetics of orofacial clefts. *Curr Opin Pediatr* 2001;13:556-60.
4. Sarkozi A, Wyszynski DF, Czeizel AE. Oral clefts with associated anomalies: findings in the Hungarian Congenital Abnormality Registry. *BMC Oral Health* 2005;5:4.
5. Derijcke A, Eerens A, Carels C. The incidence of oral clefts: a review. *Br J Oral Maxillofac Surg* 1996;34:488-94.
6. Matthews JL, Oddone-Paolucci E, Harrop RA. The epidemiology of cleft lip and palate in Canada, 1998 to 2007. *Cleft Palate Craniofac J* 2014 Jul 9 [Epub]. DOI: <http://dx.doi.org/10.1597/14-047>.
7. Genisca AE, Frias JL, Broussard CS, Honein MA, Lammer EJ, Moore CA, et al. Orofacial clefts in the National Birth Defects Prevention Study, 1997-2004. *Am J Med Genet A* 2009;149A:1149-58.

8. Fraser FC. The genetics of cleft lip and cleft palate. *Am J Hum Genet* 1970;22:336-52.
9. Shaw GM, Carmichael SL, Yang W, Harris JA, Lammer EJ. Congenital malformations in births with orofacial clefts among 3.6 million California births, 1983-1997. *Am J Med Genet A* 2004;125A:250-6.
10. Milerad J, Larson O, PhD D, Hagberg C, Ideberg M. Associated malformations in infants with cleft lip and palate: a prospective, population-based study. *Pediatrics* 1997;100(2 Pt 1):180-6.
11. Shafi T, Khan MR, Atiq M. Congenital heart disease and associated malformations in children with cleft lip and palate in Pakistan. *Br J Plast Surg* 2003;56:106-9.
12. Shprintzen RJ, Siegel-Sadewitz VL, Amato J, Goldberg RB. Anomalies associated with cleft lip, cleft palate, or both. *Am J Med Genet* 1985;20:585-95.
13. Vallino-Napoli LD, Riley MM, Halliday JL. An epidemiologic study of orofacial clefts with other birth defects in Victoria, Australia. *Cleft Palate Craniofac J* 2006;43:571-6.
14. Van der Veen FJ, van Hagen JM, Berkhof J, Don Griot JP. Regional underreporting of associated congenital anomalies in cleft patients in the Netherlands. *Cleft Palate Craniofac J* 2006;43:710-4.
15. Wyse RK, Mars M, al-Mahdawi S, Russell-Eggitt IM, Blake KD. Congenital heart anomalies in patients with clefts of the lip and/or palate. *Cleft Palate J* 1990;27:258-64.
16. Knox EG, Lancashire RJ. *Epidemiology of congenital malformations*. London: Her Majesty's Stationary Office; 1991.
17. Cordero JF. Finding the causes of birth defects. *N Engl J Med* 1994;331:48-9.