BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017963
Article Type:	Research
Date Submitted by the Author:	29-May-2017
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology, Health policy, Public health
Keywords:	birth defect, infant, fetal, mortality, maternal age

Infant and fetal mortality caused by birth defects in Korea

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Key words; birth defect, infant death, fetal death, maternal age

Running title: Infant and fetal mortality caused by birth defects in Korea

Tweetable abstract: Severe anomalies except chromosomal abnormality were the most prevalent in teenage pregnancies.

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Abstract

Objective: To analyze the prevalence of fetal and infant deaths due to birth defects in Korea and those trends according to maternal age.

Design: Retrospective national cohort study

Setting: Database in Korean vital Statistics, between 2009 and 2015.

Participants: 2,176 infant deaths and 4,343 fetal deaths caused by birth defects, among 3,181,145 total live births and 43,385 fetal deaths during study periods

Methods: Infant and fetal mortality rates (IMRs and FMRs) by birth defects, from deaths caused by birth defects, were analyzed. Those were compared, according to maternal age groups; '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).

Main Outcome Measures: IMRs and FMRs by birth defects and comparison according to maternal age group.

Results: IMRs and FMRs by birth defects were 6.84 per 10,000 live births, and 13.47 per 10,000 total births. The most common causes of infant deaths and fetal deaths by birth defect were anomaly of circulatory system (51.1%, IMR 3.5) and chromosomal abnormality (33.1%, FMR 4.46), respectively. Among groups by maternal age, FMRs by birth defects were significantly higher in group I and V, compared to it in group III, (Odd ratio (OR) 6.59, 95% CI 3.49-12.43 and 3.46, 95% CI 1.77-6.78, respectively). IMR and FMR by nervous system anomaly were significantly higher in group I, with 3.63 (OR 2.0, 95% CI 1.97-2.03) and 29.84 (OR15.04, 95% CI 3.59-62.96), compared to 0.32 and 1.97 in group III.

Conclusion: FMRs by birth defects were the highest in extreme maternal age groups. Severe anomalies except chromosomal abnormality were the most prevalent in teenage pregnancies.

Strengths and limitations of this study

- This study is the first one that reports infant and fetal mortalities caused by birth defects in Korea, from the national vital statistics.
- This study compared the infant and fetal mortalities caused by birth defects, according to maternal age group, which showed higher prevalence of them in teenage pregnancies.
- The limitation of this study is that it does not show present prevalence of birth defects in live births.
- This study supports a policy about mandatory folic acid fortification in Korea.

Introduction

Birth defects (structural abnormalities, sensory changes, chromosomal abnormalities, metabolic abnormalities, and neurodevelopmental defects) are presented in approximately 2-3% of all births [1-3]. Severe birth defects account for 20-25% of perinatal mortality and they are leading causes of infant mortality, abortion, and stillbirth [2-5]. During the last decade, screening tests and ultrasonography during pregnancy have been developed to detect birth defects. However, etiologies of 60-70% of birth defects remain unknown.

In developed countries, birth defects surveillance systems have been developed to collect data on

major structural birth defects and chromosomal abnormalities [6-8]. European registry reported that total and live birth prevalence of trisomies 21, 18 and 13 were increased between 1990 and 2009, and those were mainly associated with increasing maternal age [9].

While the number of live births in Korea has been decreased, maternal age has been increased [10, 11]. The prevalence of birth defects in Korean live births has been reported before, using the data based on the National Health Insurance Corporation on medical institutes across the country [12, 13]. However, it is important to include stillbirths and abortions in birth defects statistics with total live births because birth defects occur during intrauterine life. Although it is hard to include spontaneous abortion in the early stage of pregnancy, the investigation of fetal death related with birth defect can be useful for estimating the prevalence of birth defects. In addition, investigation of infant death related to birth defect can be valuable information for counseling parents, antenatally and postnatally.

The aim of this study was to analyze the prevalence of fetal and infant deaths associated with birth defects, which are fetal/infant mortality rates (FMR/IMR) by birth defect, and evaluate changes of those prevalence rates, according to maternal age.

Materials and Methods

This study was conducted by utilizing deidentified data about fetal deaths, infant deaths, and live births between 2009 and 2015 from 'Korean Vital Statistics' of the Korean Statistical Information Service [10]. Korean Vital Statistics is a nationwide database developed to understand birth, death, marriage, and divorce in Korea. Data from Korean Vital Statistics are released monthly and annually via a press release, on website (http://kosis.kr), and in online publications, such as 'Annual Report on Vital Statistics.' From fetal and infant deaths data, fetal

and infant death recorded as ‘a death caused by birth defect’ were included in fetal and infant deaths associated with birth defect. Fetal death was defined as intrauterine fetal death occurring after 16 weeks of gestational age and before the start of delivery or those occurring during labor. Infant death was defined as a death occurring within the first year of life.

Birth defects were categorized by birth defect group (the system affected) and subtype (individual disease) according to the 10th Revision of the International Classification of Diseases (ICD-10) and were investigated by including major groups of birth defects managed by EUROCAT, ICBDSR, and the National Birth Defects Prevention Network (NBDPN). Deaths caused by disease code ‘Q’ representing congenital disease were defined as fetal and infant deaths related TO birth defect. According to the above standards, 2,176 infant deaths and 4,343 fetal deaths were caused by birth defect. This study calculated IMR by birth defects by dividing the number of infant deaths related to birth defects by the total number of live births. It was presented as the number per 10,000 live births as a standard. FMR by birth defects was calculated by dividing the number of fetal deaths related with birth defect by the total number of live births and fetal deaths, which presented as the number per 10,000 total births. Maternal age groups were divided to the following five groups: ‘10-19 yr’ (I), ‘20-29 yr’ (II), ‘30-34 yr’ (III), ‘35-39 yr’ (IV), and ‘40-55 yr’ (V). IMRs and FMRs by birth defects in group III were used as control for comparison with IMRs/FMRs of other groups. For chromosomal abnormalites, comparison was also performed between group II and the other groups.

Statistical analysis

Statistical calculations were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA), including means, proportions, odd ratio (OR), and 95% confidence intervals (CIs). Chi-square tests were performed to compare proportions of independent variables and t-tests were performed to compare means. Statistical significance was considered at $P < 0.05$ or if the 95% CI of OR did not include 1.

Ethics statement

The study protocol was approved by the institutional review boards of Catholic University of Korea. Informed consent was waived by the board.

Results

Baseline characteristics

Total numbers of live births and fetal deaths in Korea from 2009 to 2015 were 3,181,145 and 43,385, respectively. Among 9,563 infant deaths during the 7 years, the number of infant deaths related to birth defect was 2,176, accounting for 22.8% of all infant deaths. The number of fetal deaths related to birth defects was 4,343, accounting for 10.0% of all fetal deaths. Baseline demographic characteristics are summarized in Table 1.

IMRs, by birth defect groups and subtypes

IMR by total birth defects was 6.84 per 10,000 live births (Table 2). Anomaly of the circulatory system was the most common cause of infant deaths related to birth defect, accounting for 51.1% of all infant deaths. Its IMR was 3.5 per 10,000 live births. The next most common defects in infant deaths were chromosomal anomalies (0.69 per 10,000 live births, 10.1%) and musculoskeletal system anomalies (0.65 per 10,000 live births, 9.6%). Among subtypes of birth defects, congenital diaphragmatic hernia (CDH) showed the highest IMR at 0.43 per 10,000 live births (Table 3). Among specified anomalies, lethal birth defects with the next highest IMRs were Tetralogy of Fallot (TOF) and hypoplastic left heart syndrome (HLHS) (with IMRs of 0.28 and 0.27 per 10,000 live births, respectively). Because patent ductus arteriosus cases included 81 cases whose birthweight was less than 2,500 g, patent ductus arteriosus was not counted as the next common birth defect. Among chromosomal anomalies, Down syndrome was the most common chromosomal abnormality with IMR of 0.27 per 10,000 live births (Table 4).

FMRs by birth defect groups and subtypes

FMR by total birth defects was 13.47 per 10,000 total births (live births plus stillbirths) (Table 2). The most common defects by group were chromosomal anomalies, accounting for 33.1% of fetal deaths related to birth defect, and it FMR was 4.46 per 10,000 total births. The most common birth defect subtype in fetal deaths was Down syndrome with FMR of 1.78 per 10,000 total births, and followed by other chromosomal abnormality, unspecified congenital heart

malformation, and Edward syndrome, with FMR of 1.36, 0.93 and 0.82 per 10,000 total births, respectively (Table 3&4).

IMRs and FMRs by birth defect groups, according to the maternal age group

In the analysis according to maternal age group, 2,529 live births, 113 fetal deaths not related to birth defects, and 12 fetal deaths related to birth defects were excluded due to missing values of maternal age. In infant deaths related to birth defect, anomaly of the circulatory system was most common in all age groups (Table 5, Figure 1). IMRs of chromosomal abnormality seemed to be increased in groups IV and V compared to that in group III. However, statistically significant difference was only observed between group V and group III (OR 2.00 95% CI 1.97-2.03). The IMR of nervous system anomaly was significantly higher in the youngest maternal age group (group I, 10-19 yr) with 3.63 per 10,000 live births (OR 2.0, 95% CI 1.97-2.03), compared to that in group III (0.32 per 10,000 live births). In fetal deaths related to birth defect, most FMRs by birth defects were highest in the youngest group, except for FMR by chromosomal abnormality which was significantly higher in group V compared to that in group III (OR 7.01, 95% CI, 2.09-23.52) (Table 6, Figure 2). Compared to FMR of group II, FMRs of chromosomal abnormality were significantly higher in group IV and V (OR 5.00, 95% CI, 1.10-22.84 and OR 10.52, 95% CI 2.47-44.88, respectively). FMRs by total birth defects were significantly higher in group I and V, compared to that in group III, (OR 6.59, 95% CI 3.49-12.43 and OR 3.46, 95% CI 1.77-6.78, respectively). Individually, FMRs for anomalies of nervous system and cardiovascular system, and, other and unspecified anomalies were significantly higher in group I, compared to those in group III, (OR 15.04, 95% CI 3.59-62.96; OR 10, 95%CI 1.23-78.2, and OR 8.35, 95% CI 2.52-27.67, respectively)

Discussion

It is important to know severe birth defects which can lead fetal and infant deaths and its prevalence. Previously, the prevalence of birth defects in Korea in live births in 2005 and 2006 was reported to be approximately 2.9% [12], similar to those (2-3%) of other studies [1-3]. However, the other study reported the prevalence of birth defects in Korea in 2009 and 2010 as 5.8% [13]. Although there might be methodological limitation and variations, the prevalence of birth defects in live births seems increasing. In this study, 22.8% of infant deaths of Korea were related to birth defects. IMR and FMR caused by birth defects between 2009 and 2015 were 6.84 per 10,000 live births and 13.47 per 10,000 total births, respectively.

The most common birth defect group related to infant deaths was anomaly of the circulatory system. However, the most common birth defect subtype was CDH. Despite advances in prenatal diagnosis and neonatal intensive care including extracorporeal membrane oxygenation and inhaled nitric oxide use, mortality rates due to CDH remain high, ranging from 50% to 70% with great variability between centers [14-16]. The second most common birth defect in infant deaths related to birth defect was TOF. The 10-year survival rate of TOF has been reported to be approximately 95 % [17, 18]. When we consider the prevalence of TOF in live births in Korea with 4.1-4.2 per 10,000 live births [12, 13] and the IMR by TOF with 0.28 per 10,000 live births in this study, we can speculate that nationwide infant survival rates of TOF in Korea will be approximately 93.3%, which is similar to that in the other reports [17, 18].

As expected, when IMRs and FMRs caused by birth defects were compared according to maternal age group, IMRs and FMRs due to chromosomal abnormality were higher in older

maternal age groups (IV and V) compared to those in group II or III. FMRs due to birth defects were significantly higher in groups I and V compared to those in group III (OR: 6.59, 95% CI: 3.49-12.43 and OR: 3.46, 95% CI: 1.77-6.78, respectively). FMR was much higher in group I. Especially, IMR and FMR due to anomalies of the nervous system were significantly higher in group I compared with those in group III, indicating higher prevalence of severe anomalies of nervous system in teenage pregnancies. In North America, fortification of flour and grain products became mandatory in 1998. Following folic acid fortification, prevalence of spina bifida birth in Canada fell by over 50% and that of other neural tube defects (NTDs) fell by approximately one-third [19]. In addition, the registry of 'European surveillance of congenital anomalies' has concluded that mandatory folic acid fortification is needed because the prevalence of NTDs has not decreased in Europe despite longstanding recommendations aiming at promoting periconceptional folic acid supplementation [20]. Results of Cochrane databases systematic review also showed a protective effect of daily folic acid supplementation in preventing NTDs compared to no intervention/placebo or vitamins and minerals without folic acid (risk ratio 0.31, 95% CI 0.17- 0.58); five studies; 6708 births; high quality evidence) [21]. Teenage pregnancies are more likely unplanned and exposed to alcohol, drug, sexual abuse, and nutritional imbalance. When pregnancies are complicated by birth defects in young age, they might lead to termination of pregnancy (TOP), more easily. This study demonstrated increasing trends of IMRs and FMRs due to birth defects in the youngest and oldest maternal age groups. However, high IMRs and FMRs due to birth defects in the youngest age group were more pronounced except for chromosomal abnormality. Therefore, mandatory folic acid fortification in Korea might help reduce nervous system anomalies because the youngest age group is less

likely to take periconceptional folic acid supplementation and the overall prevalence of spina bifida in Korea shows increasing tendency [13].

In Europe, increasing trend of trisomy 13, 18, and 21 between 1990 and 2009 was reported [9]. Because most TOPs with birth defects are illegal in Korea, it is almost impossible to estimate the proportions of TOP due to birth defects among fetal deaths. An international study has reported that the total mean prevalence of Down syndrome (still births, live births, and TOP) is increased from 13.1 to 18.2/10,000 births between 1993 and 2004 with increasing maternal age [22]. However, the total mean prevalence of Down syndrome births remains stable at 8.3/10,000 births, balanced by a great increase of TOP [22]. Maternal age at conception has increased in Korea, although there are race/ethnic specific variations in birth defects [23]. IMR and FMR by Down syndrome was 0.27 per 10,000 live births and 1.78 per 10,000 total births, respectively. When we assume the prevalence of Down syndrome in as 3.7-4.7 per 10,000 live births from the previous studies in Korea [12, 13], infant survival rate of Down syndrome can be estimated approximately 93.6%. Based on the increased prevalence of Down syndrome in the international study, according to increasing maternal age [22], we can expect that TOP due to Down syndrome may be also considerable in Korea.

The limitation of this study is that it does not show present prevalence of birth defects in live births. Therefore, it is necessary to establish a comprehensive surveillance system with periodic production of data and monitoring to have effective prevention and management of birth defects. The second limitation of this study is that death cause of death registry is mostly made by clinician without autopsy. Because one or two disease codes are registered as the main code in death registry, multiple anomalies might have been included in one category. Lastly, this study did not include data on maternal nationality, paternal age, educational background, antenatal care,

or parents' occupation due to high rates of missing values. However, this study is the first one that reports IMRs and FMRs caused by birth defects in Korea and different patterns according to maternal age group. Severe birth defects with high FMR were found to be more common in extreme maternal age groups (the youngest and the oldest). Except chromosomal abnormality, most severe anomalies, especially those of the nervous system and cardiovascular system, were more common in teenage pregnancies.

As maternal age at conception is getting increased in Korea and screening tools are developing, prevalence and prenatal diagnosis of chromosomal anomalies are likely to be increased. Multi-disciplinary cooperation among government, politician, clinicians, and non-governmental organization is urgent not only for increasing fertility rate, but also for increasing heathy pregnancies with effective prevention and management of birth defects, especially for extreme maternal age groups and for supporting complicated pregnancies. A mandatory folic acid fortification needs to be discussed and considered in Korea.

Author contributions

We confirm that all the authors have made substantive intellectual contributions to the paper; they understand their role in taking responsibility and being accountable for what is published. JCS conceptualized and reviewed the paper. HSK conceptualized the paper, gathered the results, analyzed the data and wrote the article. YHC, JHW, SKC, and IYP analyzed the data and reviewed the paper. YGP performed statistical analysis of the data.

Funding

This study was supported by Research Fund of Seoul St. Mary's Hospital, The Catholic University of Korea.

Conflict of Interest

All authors have no conflict of interest related with this article.

Details of ethics approval

We obtained approval from the institutional review boards of Catholic University of Korea.

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Table 1. Demographic characteristics of total live births, total fetal deaths, total infant deaths, and fetal/infant deaths related with birth defect

Parameters	Total live births	Total fetal deaths	Total infant deaths	Infant deaths by birth defects	Fetal deaths by birth defects
	n=3,181,145	n=43,385	n=9563	n=2,176	n=4,343
Maternal age (yr)	31.85 ± 26.72	30.69 ± 6.16	31.57 ± 4.97	31.68 ± 4.86	21.2 ± 4.42
Gestational age (weeks)	38.58 ± 2.3	20.13 ± 5.83	32.24 ± 6.453	35.88 ± 4.36	31.8 ± 5.59
Birthweight (kg)	3.21 ± 0.48	0.69 ± 0.78	1.96 ± 1.15	2.47 ± 0.87	0.51 ± 0.5
Multiple birth n (%)	101,797 (3.2)	3,818 (8.8)	1492 (15.6)	196 (9))	200 (4.6)

Data are mean ± standard deviation or no. (%) unless otherwise specified.

Table 2. Korean prevalence of fetal deaths and infant deaths caused by birth defect groups in 2009-2015

Birth defects (ICD-10)	Total N. of fetal and infant deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10,000 live births and fetal deaths	N. of infant deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10,000 live births	N. of fetal deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10,000 total births
Nervous system (Q00-07)	970	14.88	3.01	136	6.25	0.43	834	19.20	2.59
Eye, ear, face and neck (Q10-18)	8	0.12	0.02	1	0.05	0.00	7	0.16	0.02
Circulatory system (Q20-28)	1605	24.62	4.98	1112	51.10	3.50	493	11.35	1.53
Respiratory system (Q30-34)	115	1.76	0.36	87	4.00	0.27	28	0.64	0.09
Cleft lip/ palate (Q35-37)	67	1.03	0.21	3	0.14	0.01	64	1.47	0.20
Digestive system (Q38-45)	203	3.11	0.63	169	7.77	0.53	34	0.78	0.11
Genital organs (Q50-56)	5	0.08	0.02	0	0.00	0.00	5	0.12	0.02
Urinary system (Q60-64)	213	3.27	0.66	54	2.48	0.17	159	3.66	0.49
Musculoskeletal system (Q65-79)	384	5.89	1.19	208	9.56	0.65	176	4.05	0.55
Other and unspecified (Q80-89)	1291	19.80	4.00	186	8.55	0.58	1105	25.44	3.43
Chromosomal abnormalities (Q90-99)	1658	25.43	5.14	220	10.11	0.69	1438	33.11	4.46
Total	6519	100.00	20.22	2176	100.00	2.64	4343	100.00	13.47

ICD, International classification of diseases, 10th revision.

Table 4. Prevalence of infant and fetal deaths caused by major chromosomal abnormalities in Korea, 2009-2015

Chromosomal birth defects	Total N. of cases caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 total births	N. of infant deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 live births	N. of fetal deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 total births
Down's syndrome	659	10.11	2.04	85	3.91	0.27	574	13.22	1.78
Trisomy 18	340	5.22	1.05	76	3.49	0.24	264	6.08	0.82
Trisomy 13	62	0.95	0.19	21	0.97	0.07	41	0.94	0.13
Kleinfelter's syndrome	33	0.51	0.10	0	0.00	0.00	33	0.76	0.10
Turner's syndrome	51	0.78	0.16	0	0.00	0.00	51	1.17	0.16
Other sex chromosome abnormalities	14	0.21	0.04	0	0.00	0.00	14	0.32	0.04
Triploidy	14	0.21	0.04	0	0.00	0.00	14	0.32	0.04
Wolff-Hirschorn syndrome	5	0.08	0.02	2	0.09	0.01	3	0.07	0.01
Cri-du-chat syndrome	5	0.08	0.02	2	0.09	0.01	3	0.07	0.01
Other chromosomal abnomalities	475	7.29	1.47	34	1.56	0.11	441	10.15	1.37
Total	1658	25.43	5.14	220	10.11	0.69	1438	33.11	4.46

Table 5. Comparison of infant mortality by birth defect according to maternal age group

	IMR								
Maternal age group Birth defects (ICD-10)	I (10-19 y)	OR (95% CI)	II (20-29 y)	OR (95% CI)	III (30-34 y)	IV (35-39 y)	OR OR (95% CI)	V (40-50 y)	OR OR (95% CI)
Nervous system (Q00-07)	3.63	**2 (1.97-2.03)**	0.42		0.32	0.52		1.21	
Eye, ear, face and neck (Q10-18)	0.00		0.00		0.01	0.00		0.00	
Circulatory system (Q20-28)	7.25		3.29		3.25	4.10		6.04	
Respiratory system (Q30-34)	0.00		0.23		0.24	0.32		1.21	
Cleft lip/ palate (Q35-37)	0.00		0.00		0.02	0.00		0.00	
Digestive system (Q38-45)	0.52		0.57		0.48	0.63		0.40	
Urinary system (Q60-64)	0.52		0.18		0.14	0.15		0.67	
Musculoskeletal system (Q65-79)	0.00		0.60		0.64	0.84		0.67	
Other and unspecified (Q80-89)	1.55		0.46		0.56	0.73		1.61	
Chromosomal abnormalities (Q90-99)	0.00		0.48		0.50	1.27		3.63	**2 (1.97-2.03)**
Total	13.47		6.22		6.16	8.56		15.44	

ICD, International classification of diseases, 10th revision; IMR, Infant mortality rate; OR, odd ratio; CI, confidence interval. IMRs by birth defects in group III were used as a reference for comparison with IMRs of other groups. Statistically significant values were presented.

Table 6. Comparison of fetal mortality by birth defect according to maternal age group

	FMR									
Maternal age group	I	OR	II	OR	III	OR	IV	OR	V	OR
Birth defects (ICD-10)	(10-19 y)	(95% CI)	(20-29 y)	(95% CI)	(30-34 y)	(95% CI)	(35-39 y)	OR (95% CI)	(40-50 y)	OR (95% CI)
Nervous system (Q00-07)	29.84	**15.04 (3.59-62.96)**	2.63	·	1.97		2.64	·	5.97	·
Eye, ear, face and neck (Q10-18)	0.45	·	0.03	·	0.01		0.02	·	0.13	·
Circulatory system (Q20-28)	9.95	**10 (1.23-78.20)**	1.48	·	1.34		1.83	·	1.43	·
Respiratory system (Q30-34)	0.45	·	0.12	·	0.06		0.09	·	0.00	·
Cleft lip/ palate (Q35-37)	0.00	·	0.27	·	0.18		0.17	·	0.13	·
Digestive system (Q38-45)	1.36	·	0.12	·	0.06		0.13	·	0.13	·
Genital organs (Q50-56)	0.51	·	0.01	·	0.02		0.02	·	0.00	·
Urinary system (Q60-64)	0.00	·	0.52	·	0.49		0.31	·	1.17	·
Musculoskeletal system (Q65-79)	0.90	·	0.64	·	0.49		0.50	·	0.26	·
Other and unspecified (Q80-89)	24.87	**8.35 (2.52-27.67)**	3.40	·	2.66		4.13	·	7.92	·
Chromosomal abnormalities (Q90-99)	4.07	·	1.87	·	3.39		10.11	·	20.64	**7.01 (2.09-23.52)**
Chromosomal abnormalities (Q90-99)*	4.07	·	1.87	·	3.39	·	10.11	**5 (1.10-22.84)**	20.64	**10.52 (2.47-44.88)**
Total	71.89	**6.59 (3.49-12.43)**	11.07	·	10.68		19.95	·	37.78	**3.46 (1.77-6.78)**

ICD, International classification of diseases, 10th revision; FMR, fetal mortality rate; OR, odd ratio; CI, confidence interval. FMRs by birth defects in group III were used as a reference for comparison with FMRs of other groups. *Comparison was performed between group II (reference) and the other groups. Statistically significant values were presented.

Table 3. Korean prevalence of fetal deaths and infant deaths caused by birth defect subtypes in 2009-2015

Birth defects (ICD-10)	N. of infant deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 livebirths	N. of fetal deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 total births
Nervous system (Q00-07)						
Anencephaly (Q00.0-00.2)	37	1.70	0.12	213	4.90	0.66
Encephalocele (Q01.0-01.9)	3	0.14	0.01	32	0.74	0.10
Congenital Hydrocephalus (Q03.0-03.9)	34	1.56	0.11	157	3.62	0.49
Holoprosencephaly (Q04.0-04.2)	14	0.64	0.04	46	1.06	0.14
Other brain anomaly (Q43-49)	36	1.65	0.11	131	3.02	0.41
Spina bifida (Q05.0-05.9)	8	0.37	0.03	28	0.64	0.09
Other spinal anomaly (Q68-69)	0	0.00	0.00	3	0.07	0.01
Arnold-Chiari malformation (Q70)	1	0.05	0.00	18	0.41	0.06
Other nervous system anomaly (Q78-79)	3	0.14	0.01	206	4.74	0.64
Eye, ear, face and neck (Q10-18)	1	0.05	0.00	7	0.16	0.02
Circulatory system (Q20-28)						
Truncus arteriosus (Q20.0)	9	0.41	0.03	1	0.02	0.00
Double outlet right ventricle	66	3.03	0.21	7	0.16	0.02
Transposition of great arteries (Q20.1-20.3)	72	3.31	0.23	0	0.00	0.00
Double inlet ventricle (Q20.4)	58	2.67	0.18	1	0.02	0.00
Discordant atrioventricular connection (Q20.5)	2	0.09	0.01	1	0.02	0.00
Isomerism of atrial appendages (Q20.6)	3	0.14	0.01	1	0.02	0.00
Ventricular septal defect (Q21.0)	50	2.30	0.16	20	0.46	0.06
Atrial septal defect (Q21.1)	20	0.92	0.06	2	0.05	0.01
Atrioventricular septal defect (Q21.2)	72	3.31	0.23	4	0.09	0.01
Tetralogy of Fallot (Q21.3)	88	4.04	0.28	21	0.48	0.07
Other malformations of cardiac septa (Q21.4, 21.8, 21.9)	6	0.28	0.02	10	0.23	0.03
Pulmonary valve atresia/stenosis (Q22.0-22.1)	52	2.39	0.16	1	0.02	0.00
Congenital tricuspid stenosis (Q22.4)	5	0.23	0.02	1	0.02	0.00
Ebstein's anomaly (Q22.5)	23	1.06	0.07	7	0.16	0.02
Hypoplastic right heart syndrome (Q22.6)	1	0.05	0.00	1	0.02	0.00
Other malformations of tricuspid valve (Q22.8, 22.9)	3	0.14	0.01	4	0.09	0.01
Aortic valve stenosis/insufficiency (Q23.0, 23.1)	9	0.41	0.03	3	0.07	0.01
Mitral valve stenosis/insufficiency (Q23.2, 23.3)	8	0.37	0.03	0	0.00	0.00

Hypoplastic left heart syndrome (Q23.4)	86	3.95	0.27	7	0.16	0.02
Dextrocardia (Q 24.0)	0	0.00	0.00	3	0.07	0.01
Cor triatriaum (Q 24.2)	2	0.09	0.01	0	0.00	0.00
Subaortic stenosis (Q 24.4)	2	0.09	0.01	0	0.00	0.00
Malformation of coronary vessels (Q24.5-24.6)	6	0.28	0.02	0	0.00	0.00
Other heart malformation (Q24.2, 24.4-24.6)	88	4.04	0.28	50	1.15	0.16
Unspecified heart malformation (Q24.9)	75	3.45	0.24	299	6.88	0.93
Patent ductus arteriosus (Q25.0)*	87	4.00	0.27	0	0.00	0.00
Coarctation/atresia/stenosis of aorta (Q25.1-25.3)	55	2.53	0.17	0	0.00	0.00
Other malformations of aorta (Q25.4)	18	0.83	0.06	4	0.09	0.01
Pulmonary artery atresia/stenosis (Q25.5, 25.6)	22	1.01	0.07	2	0.05	0.01
Total anomalous pulmonary venous connection (Q26.2)	83	3.81	0.26	0	0.00	0.00
Partial anomalous pulmonary venous connection (Q26.3)	3	0.14	0.01	1	0.02	0.00
Peripheral arteriovenous malformation (Q27.3, 27.9, 27.9)	1	0.05	0.00	4	0.09	0.01
Malformations of cerebral vessels (Q 28.2, 28.3)	6	0.28	0.02	4	0.09	0.01
Other malformations of circulatory system (Q20.8, 20.9, 22.3, 25.7-26.1, 26.4, 27.0, 26.8, 28,8, 28.9)	31	1.42	0.10	34	0.78	0.11
Respiratory system (Q30-34)						
Other malformations of larynx, bronchus, trachea (Q31.0-32.4)	34	1.56	0.11	3	0.07	0.01
Congenital cystic lung (Q33.0)	5	0.23	0.02	5	0.12	0.02
Other malformation of lung (Q33.1-33.9)	42	1.93	0.13	16	0.37	0.05
Other malformations of respiratory system (Q34)	6	0.28	0.02	4	0.09	0.01
Cleft lip/palate (Q35-37)	3	0.14	0.01	64	1.47	0.20
Digestive system (Q38-45)						
Other malformation of mouths (Q38.5)	0	0.00	0.00	1	0.02	0.00
Esophageal atresia/stenosis (Q39.0-39.2)	34	1.56	0.11	6	0.14	0.02
Malformation of upper elimentary tract (Q40.0-40.9)	3	0.14	0.01	3	0.07	0.01
Duodenal atresia/stenosis (Q41.0)	3	0.14	0.01	7	0.16	0.02
Small intestine atresia/stenosis (Q41.1-41.9)	22	1.01	0.07	1	0.02	0.00
Anorectal atresia/stenosis (Q42.0-42.3)	2	0.09	0.01	2	0.05	0.01
Congenital megacolon (Q43.1)	44	2.02	0.14	0	0.00	0.00
Malrotation of colon (Q43.3)	9	0.41	0.03	0	0.00	0.00
Persistent cloaca (Q43.7)	1	0.05	0.00	2	0.05	0.01
Other intestinal and bile duct malformation (Q43.8-44.3)	42	1.93	0.13	6	0.14	0.02

Liver malformation (Q44.7)	4	0.18	0.01	0	0.00	0.00
Other malformation of digestive system (Q 42.8, 43.0, 45.8, 45.9)	5	0.23	0.02	6	0.14	0.02
Genital organs (Q50-56)	0	0.00	0.00	5	0.12	0.02
Urinary system (Q60-64)						
Renal agenesis (Q60.0-60.6)	22	1.01	0.07	44	1.01	0.14
Autosomal recessive polycystic kidney (Q61.1)	10	0.46	0.03	6	0.14	0.02
Unspecified polycystic kidney (Q61.3)	6	0.28	0.02	23	0.53	0.07
Renal dysplasia (Q61.4)	6	0.28	0.02	30	0.69	0.09
Cystic kidney (Q61.0, Q61.5-61.9)	1	0.05	0.00	3	0.07	0.01
Congenital hydronephrosis (Q62.0-62.8)	2	0.09	0.01	14	0.32	0.04
Other renal anomaly (Q63.0, 63.2, 63.8, 63.9)	3	0.14	0.01	30	0.69	0.09
Posterior urethral valve (Q64.2)	3	0.14	0.01	3	0.07	0.01
Congenital absence of bladder and urethra (Q64.5-64.9)	1	0.05	0.00	6	0.14	0.02
Musculoskeletal system (Q65-79)						
Club foot-talipes equinovarus (66.0)	0	0.00	0.00	1	0.02	0.00
Other congenital feet deformities (Q66.1-66.9)	0	0.00	0.00	4	0.09	0.01
Congenital deformities of skull, face, and jaw (Q67.0-67.4)	0	0.00	0.00	2	0.05	0.01
Pectus carinatum (Q67.6)	2	0.09	0.01	0	0.00	0.00
Other congenital musculoskeletal deformities (Q68.0-Q70.9)	0	0.00	0.00	12	0.28	0.04
Total limb reduction defects (Q71.0-71.9, Q72.0-72.9, Q73.0-73.8)	0	0.00	0.00	8	0.18	0.02
Other malformation of limbs and pelvic girdle (Q74.0-Q74.2, 74.8)	3	0.14	0.01	19	0.44	0.06
Arthrogryposis multiplex congenita (Q74.3)	4	0.18	0.01	1	0.02	0.00
Craniosynostosis (Q75.0)	6	0.28	0.02	0	0.00	0.00
Malformations of skul and face bones (Q75.1-75.9)	6	0.28	0.02	7	0.16	0.02
Klippel-Feil syndrome (Q76.1)	2	0.09	0.01	0	0.00	0.00
Malformations of spine and bony thorax (Q76.2-76.9)	2	0.09	0.01	7	0.16	0.02
Achondrogenesis/Hypochondrogenesis (Q77.0)	2	0.09	0.01	1	0.02	0.00
Thanatophoric dysplasia (Q77.1)	7	0.32	0.02	20	0.46	0.06
Asphyxiating thoracic dysplasia (Q77.2)	1	0.05	0.00	3	0.07	0.01
Achondroplasia/hypochondroplasia (Q77.4)	3	0.14	0.01	9	0.21	0.03
Osteogenesis imperfecta (Q78.0)	2	0.09	0.01	6	0.14	0.02
Other osteochondrodysplasia (Q77.8, 78.8, 78.9)	2	0.09	0.01	4	0.09	0.01

Diaphragmatic hernia (Q79.0)	138	6.34	0.43	22	0.51	0.07
Other malformations of diaphragm (Q79.1)	6	0.28	0.02	1	0.02	0.00
Omphalocele (Q79.2)	10	0.46	0.03	15	0.35	0.05
Gastroschisis (Q79.3)	8	0.37	0.03	12	0.28	0.04
Prune belly syndrome (Q79.4)	0	0.00	0.00	3	0.07	0.01
Other musculoskeletal anomaly (Q79.8, 79.9)	4	0.18	0.01	19	0.44	0.06
Other and unspecified (Q80-89)	186	8.55	0.58	1105	25.44	3.43
Chromosomal abnormalities (Q90-99)	220	10.11	0.69	1438	33.11	4.46

*Patent ductus arteriosus cases included 81 cases whose birthweight was less than 2,500 g.

N, number.

Figure 1. Infant mortality caused by birth defects, according to maternal age group.
Maternal age groups: ‘10-19 yr’ (I), ‘20-29 yr’ (II), ‘30-34 yr’ (III), ‘35-39 yr’ (IV), and ‘40-55 yr’ (V).

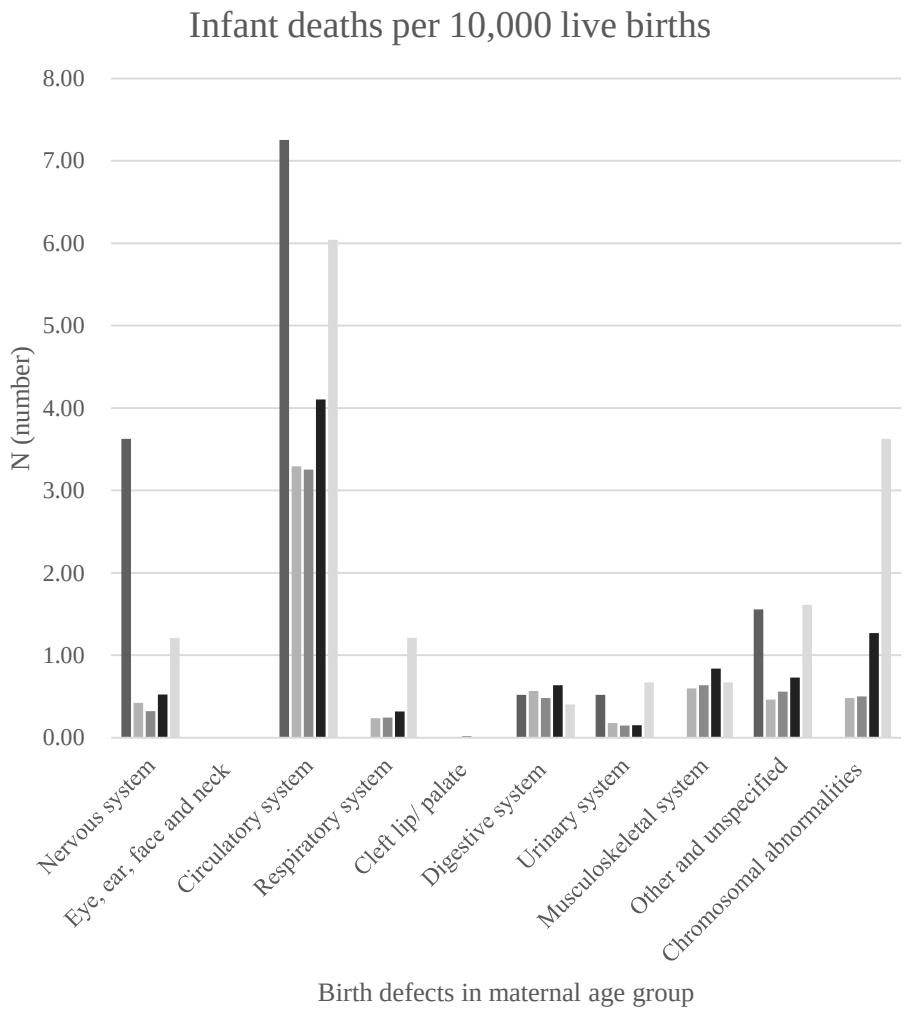
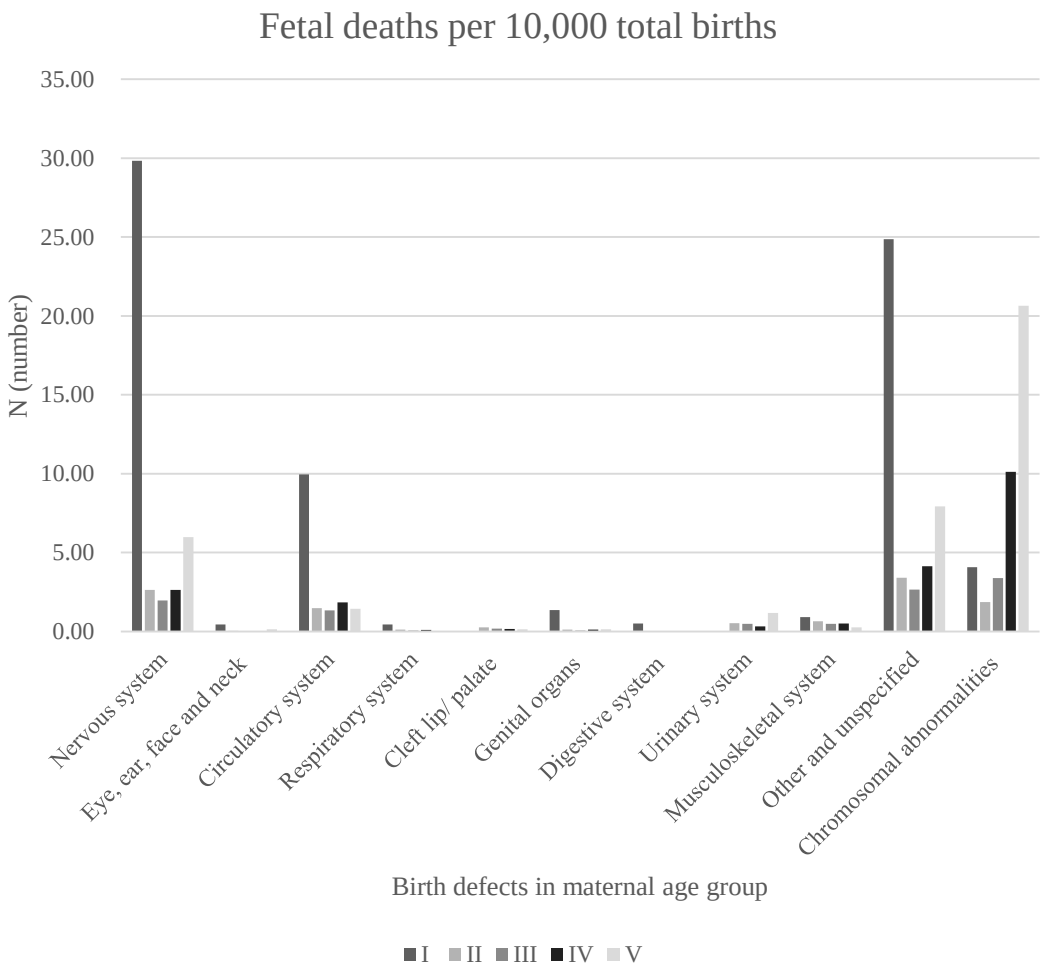


Figure 2. Fetal mortality caused by birth defects, according to maternal age group.
Maternal age groups: '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Infant and fetal mortality caused by birth defects in Korea: retrospective national cohort study
		(*b*) abstract: Page 2
Introduction		
Background/rationale	2	Page 3-4
Objectives	3	Page 4
Methods		
Study design	4	Retrospective national cohort study
Setting	5	Database in Korean vital Statistics, between 2009 and 2015.
Participants	6	(*a*) *Cohort study*— 2,176 infant deaths and 4,343 fetal deaths caused by birth defects, among 3,181,145 total live births and 43,385 fetal deaths between 2009 and 2015 in Korean vital statistics. Page 4-5
Variables	7	This study calculated infant mortality rate (IMR) by birth defects by dividing the number of infant deaths related to birth defects by the total number of live births. It was presented as the number per 10,000 live births as a standard. Fetal mortality rate (FMR) by birth defects was calculated by dividing the number of fetal deaths related with birth defect by the total number of live births and fetal deaths, which presented as the number per 10,000 total births. Maternal age groups were divided to the following five groups: '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V). IMRs and FMRs by birth defects in group III were used as control for comparison with IMRs/FMRs of other groups.: Page 5
Data sources/ measurement	8*	Maternal age groups were divided to the following five groups: '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V). IMRs and FMRs by birth defects in group III were used as control for comparison with IMRs/FMRs of other groups. Page 5
Bias	9	The limitation of this study is that it does not show present prevalence of birth defects in live births. Therefore, it is necessary to establish a comprehensive surveillance system with periodic production of data and monitoring to have effective prevention and management of birth defects. The second limitation of this study is that death cause of death registry is mostly made by clinician without autopsy. Because one or two disease codes are registered as the main code in death registry, multiple anomalies might have been included in one category. Lastly, this study did not include data on maternal nationality, paternal age, educational background, antenatal care, or parents' occupation due to high rates of missing values. Page 11

Study size	10	2,176 infant deaths and 4,343 fetal deaths caused by birth defects, among 3,181,145 total live births and 43,385 fetal deaths between 2009 and 2015 in Korean vital statistics.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Maternal age groups were divided to the following five groups: '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V). IMRs and FMRs by birth defects in group III were used as control for comparison with IMRs/FMRs of other groups, because IMRs and FMRs were lowest in group III. Page 5
Statistical methods	12	(*a*) Statistical calculations were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA), including means, proportions, odd ratio (OR), and 95% confidence intervals (CIs). Chi-square tests were performed to compare proportions of independent variables and t-tests were performed to compare means. Statistical significance was considered at $P < 0.05$ or if the 95% CI of OR did not include 1. (*b*) In the analysis according to maternal age group, 2,529 live births, 113 fetal deaths not related to birth defects, and 12 fetal deaths related to birth defects were excluded due to missing values of maternal age.

Continued on next page

Results		
Participants	13*	2,176 infant deaths and 4,343 fetal deaths caused by birth defects, among 3,181,145 total live births and 43,385 fetal deaths between 2009 and 2015 in Korean vital statistics.
Descriptive data		Total numbers of live births and fetal deaths in Korea from 2009 to 2015 were 3,181,145 and 43,385, respectively. Among 9,563 infant deaths during the 7 years, the number of infant deaths related to birth defect was 2,176, accounting for 22.8% of all infant deaths. The number of fetal deaths related to birth defects was 4,343, accounting for 10.0% of all fetal deaths. Baseline demographic characteristics are summarized in Table 1. (page 6)
Outcome data	15*	IMRs and FMRs by birth defects and comparison according to maternal age group.
Main results	16	IMRs and FMRs by birth defects were 6.84 per 10,000 live births, and 13.47 per 10,000 total births. The most common causes of infant deaths and fetal deaths by birth defect were anomaly of circulatory system (51.1%, IMR 3.5) and chromosomal abnormality (33.1%, FMR 4.46), respectively. Among groups by maternal age, FMRs by birth defects were significantly higher in group I and V, compared to it in group III, (Odd ratio (OR) 6.59, 95% CI 3.49-12.43 and 3.46, 95% CI 1.77-6.78, respectively). IMR and FMR by nervous system anomaly were significantly higher in group I, with 3.63 (OR 2.0, 95% CI 1.97-2.03) and 29.84 (OR15.04, 95% CI 3.59-62.96), compared to 0.32 and 1.97 in group III.
Other analyses	17	
Discussion		
Key results	18	FMRs by birth defects were the highest in extreme maternal age groups. Severe anomalies except chromosomal abnormality were the most prevalent in teenage pregnancies.
Limitations	19	The limitation of this study is that it does not show present prevalence of birth defects in live births. Therefore, it is necessary to establish a comprehensive surveillance system with periodic production of data and monitoring to have effective prevention and management of birth defects. The second limitation of this study is that death cause of death registry is mostly made by clinician without autopsy. Because one or two disease codes are registered as the main code in death registry, multiple anomalies might have been included in one category. Lastly, this study did not include data on maternal nationality, paternal age, educational background, antenatal care, or parents' occupation due to high rates of missing values.
Interpretation	20	However, this study is the first one that reports IMRs and FMRs caused by birth defects in Korea and different patterns according to maternal age group. Severe birth defects with high FMR were found to be more common in extreme maternal age groups (the youngest and the oldest). Except chromosomal abnormality, most severe anomalies, especially those of the nervous system and cardiovascular system, were more common in teenage pregnancies.
Generalisability	21	The most common birth defect group related to infant deaths was anomaly of the circulatory system. However, the most common birth defect subtype was CDH. Despite advances in prenatal diagnosis and neonatal intensive care including extracorporeal membrane oxygenation and inhaled nitric oxide use, mortality rates due to CDH remain high, ranging from 50% to

		70% with great variability between centers [14-16]. The second most common birth defect in infant deaths related to birth defect was TOF. The 10-year survival rate of TOF has been reported to be approximately 95 % [17, 18]. When we consider the prevalence of TOF in live births in Korea with 4.1-4.2 per 10,000 live births [12, 13] and the IMR by TOF with 0.28 per 10,000 live births in this study, we can speculate that nationwide infant survival rates of TOF in Korea will be approximately 93.3%, which is similar to that in the other reports [17, 18].
Other information		
Funding	22	This study was supported by Research Fund of Seoul St. Mary's Hospital, The Catholic University of Korea.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

A national cohort study evaluating infant and fetal mortality caused by birth defects in Korea

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017963.R1
Article Type:	Research
Date Submitted by the Author:	31-Aug-2017
Complete List of Authors:	Ko, Hyun Sun; Catholic University of Korea School of Medicine, Kim, Dong Joo; Catholic University of Korea, obstetrics and gynecology; St. Mary's women's hospital, Obstetrics and gynecology Chung, Yoohyun; Catholic University of Korea School of Medicine Wie, Jeong Ha; Catholic University of Korea School of Medicine Choi, Sae Kyung; Catholic University of Korea School of Medicine Park, In Yarg; Catholic University of Korea School of Medicine Park, Yong Gyu; Catholic University of Korea School of Medicine Shin, Jong Chul; Catholic University of Korea School of Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology, Health policy, Public health
Keywords:	birth defect, infant, fetal, mortality, maternal age

A national cohort study evaluating infant and fetal mortality caused by birth defects in Korea

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Key words; birth defect, infant death, fetal death, maternal age

Running title: Infant and fetal mortality caused by birth defects in Korea

Tweetable abstract: Severe anomalies except chromosomal abnormality were the most prevalent in teenage pregnancies.

Abstract

Objective: To analyze the prevalence of fetal and infant deaths due to birth defects in Korea and those trends according to maternal age.

Design: Retrospective national cohort study

Setting: Database in Korean vital Statistics, between 2009 and 2015.

Participants: 2,176 infant deaths and 4,343 fetal deaths caused by birth defects, among 3,181,145 total live births and 43,385 fetal deaths during study periods

Methods: Infant and fetal mortality rates (IMRs and FMRs) by birth defects, from deaths caused by birth defects, were analyzed. Those were compared, according to maternal age groups; '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).

Main Outcome Measures: IMRs and FMRs by birth defects and comparison according to maternal age group.

Results: IMRs and FMRs by birth defects were 6.84 per 10,000 live births, and 13.47 per 10,000 total births. The most common causes of infant deaths and fetal deaths by birth defect were anomaly of circulatory system (51.1%, IMR 3.5) and chromosomal abnormality (33.1%, FMR 4.46), respectively. Among groups by maternal age, FMRs by birth defects were significantly higher in group I and V, compared to it in group III, (Odd ratio (OR) 6.59, 95% CI 3.49-12.43 and 3.46, 95% CI 1.77-6.78, respectively). IMR and FMR by nervous system anomaly were significantly higher in group I, with 3.63 (OR 2.0, 95% CI 1.97-2.03) and 29.84 (OR15.04, 95% CI 3.59-62.96), compared to 0.32 and 1.97 in group III.

Conclusion: FMRs by birth defects were the highest in extreme maternal age groups. Severe anomalies except chromosomal abnormality were the most prevalent in teenage pregnancies.

Strengths and limitations of this study

- This study is the first one that reports infant and fetal mortalities caused by birth defects in Korea, from the national vital statistics.
- This study compared the infant and fetal mortalities caused by birth defects, according to maternal age group, which showed higher prevalence of them in teenage pregnancies.
- The limitation of this study is that death cause of fetal/infant deaths were mostly diagnosed clinically without autopsy and there is no available data about spontaneous or induced abortion in fetal deaths.

- The limitation of this study is that it does not show present prevalence of birth defects in live births.

Introduction

Birth defects (structural abnormalities, sensory changes, chromosomal abnormalities, metabolic abnormalities, and neurodevelopmental defects) are presented in approximately 2-3% of all births [1-3]. Severe birth defects account for 20-25% of perinatal mortality and they are leading causes of infant mortality, abortion, and stillbirth [2-5]. During the last decade, screening tests and ultrasonography during pregnancy have been developed to detect birth defects. However, etiologies of 60-70% of birth defects remain unknown.

In developed countries, birth defects surveillance systems have been developed to collect data on major structural birth defects and chromosomal abnormalities [6-8]. European registry reported that total and live birth prevalence of trisomies 21, 18 and 13 were increased between 1990 and 2009, and those were mainly associated with increasing maternal age [9].

While the number of live births in Korea has been decreased, maternal age has been increased [10, 11]. The prevalence of birth defects in Korean live births has been reported before, using the data based on the National Health Insurance Corporation on medical institutes across the country [12, 13]. However, it is important to include stillbirths and abortions in addition to live births to account for all pregnancies within birth defects. Although it is hard to include spontaneous abortion in the early stage of pregnancy, the

investigation of fetal death related with birth defect can be useful for estimating the prevalence of birth defects. In addition, investigation of infant death related to birth defect can be valuable information for counseling parents, antenatally and postnatally.

The aim of this study was to analyze the prevalence of fetal and infant deaths associated with birth defects, which are fetal/infant mortality rates (FMR/IMR) by birth defect, and evaluate changes of those prevalence rates, according to maternal age.

Materials and Methods

This national cohort study was conducted by utilizing deidentified data about fetal deaths, infant deaths, and live births between 2009 and 2015 from 'Korean Vital Statistics' of the Korean Statistical Information Service [10]. Korean Vital Statistics is a nationwide database developed to understand birth, death, marriage, and divorce in Korea. Data from Korean Vital Statistics are released monthly and annually via a press release, on website (http://kosis.kr), and in online publications, such as 'Annual Report on Vital Statistics.' Since 2007, surveys and statistical analysis methods for infant and maternal death have been revised and complemented [14] to develop into a method for calculating more concrete, accurate numbers for fetal, infant, and maternal mortality rates in Korea. In summary, revision and supplementation of the statistics for fetal, infant and maternal death have been performed and validated by combination of official death registry data for vital statistics, survey data of public health center or medical institution, medical insurance claims database of the National Health Insurance Corporation on medical institutes across the country, and cremation reports data. Because national data about fetal death has been included since 2009, study cohort for this study was made by data between 2009 and 2015. However, data did not include information whether the cause of death was proven by autopsy. From fetal

and infant deaths data, fetal and infant death recorded as ‘a death caused by birth defect’ were included in fetal and infant deaths associated with birth defect. Fetal deaths recorded as ‘termination of pregnancy (TOP)’ were excluded. Fetal death was defined as intrauterine fetal death occurring after 16 weeks of gestational age and before the start of delivery or those occurring during labor. Infant death was defined as a death occurring within the first year of life.

Birth defects were categorized by birth defect group (the system affected) and subtype (individual disease) according to the 10th Revision of the International Classification of Diseases (ICD-10) and were investigated by including major groups of birth defects managed by EUROCAT, ICBDSR, and the National Birth Defects Prevention Network (NBDPN). Deaths caused by disease code ‘Q’ representing congenital disease were defined as fetal and infant deaths related to birth defect. According to the above standards, 2,176 infant deaths and 4,343 fetal deaths were caused by birth defect. This study calculated IMR by birth defects by dividing the number of infant deaths related to birth defects by the total number of live births. It was presented as the number per 10,000 live births as a standard. FMR by birth defects was calculated by dividing the number of fetal deaths related with birth defect by the total number of live births and fetal deaths, which presented as the number per 10,000 total births. Maternal age groups were divided to the following five groups: ‘10-19 yr’ (I), ‘20-29 yr’ (II), ‘30-34 yr’ (III), ‘35-39 yr’ (IV), and ‘40-55 yr’ (V). IMRs and FMRs by birth defects in group III were used as control for comparison with IMRs/FMRs of other groups. For chromosomal abnormalities, comparison was also performed between group II and the other groups.

Statistical analysis

Statistical calculations were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA), including means, proportions, odd ratio (OR), and 95% confidence intervals (CIs). Chi-square tests were performed to compare proportions of independent variables and t-tests were performed to compare means. One decimal place was marked up in the presentation of maternal ages and gestational ages. Statistical significance was considered at $P < 0.05$ or if the 95% CI of OR did not include 1.

Ethics statement

The study protocol was approved by the institutional review board of Catholic University of Korea (KC17ZESI0409). Informed consent was waived by the board.

Results

Baseline characteristics

Total numbers of live births and fetal deaths in Korea from 2009 to 2015 were 3,181,145 and 43,385, respectively. Among 9,563 infant deaths during the 7 years, the number of infant deaths related to birth defect was 2,176, accounting for 22.8% of all infant deaths. 759 fetal deaths (1.75% of all fetal deaths) recorded as 'TOP' were excluded. The number of fetal deaths related to birth defects was 4,343, accounting for 10.0% of all fetal deaths. Baseline demographic characteristics are summarized in Table 1.

IMRs, by birth defect groups and subtypes

IMR by total birth defects was 6.84 per 10,000 live births (Table 2). Anomaly of the circulatory system was the most common cause of infant deaths related to birth defect, accounting for 51.1% of all infant deaths. Its IMR was 3.5 per 10,000 live births. The next most common defects in infant deaths were chromosomal anomalies (0.69 per 10,000 live births, 10.1%) and musculoskeletal system anomalies (0.65 per 10,000 live births, 9.6%). Among subtypes of birth defects, congenital diaphragmatic hernia (CDH) showed the highest IMR at 0.43 per 10,000 live births (supplementary material). Among specified anomalies, lethal birth defects with the next highest IMRs were Tetralogy of Fallot (TOF) and hypoplastic left heart syndrome (HLHS) (with IMRs of 0.28 and 0.27 per 10,000 live births, respectively). Among chromosomal anomalies, Down syndrome was the most common chromosomal abnormality with IMR of 0.27 per 10,000 live births (Table 3).

FMRs by birth defect groups and subtypes

FMR by total birth defects was 13.47 per 10,000 total births (live births plus stillbirths) (Table 2). The most common defects by group were chromosomal anomalies, accounting for 33.1% of fetal deaths related to birth defect, and it FMR was 4.46 per 10,000 total births. The most common birth defect subtype in fetal deaths was Down syndrome with FMR of 1.78 per 10,000 total births, and followed by other chromosomal abnormality, unspecified congenital heart malformation, and Edward syndrome, with FMR of 1.36, 0.93 and 0.82 per 10,000 total births, respectively (Table 3 and supplementary material).

IMRs and FMRs by birth defect groups, according to the maternal age group

In the analysis according to maternal age group, 2,529 live births, 113 fetal deaths not related to birth defects, and 12 fetal deaths related to birth defects were excluded due to missing values of maternal age. In infant deaths related to birth defect, anomaly of the circulatory system was most common in all age groups (Table 4, Figure 1). IMRs of chromosomal abnormality seemed to be increased in groups IV and V compared to that in group III. However, statistically significant difference was only observed between group V and group III (OR 2.00 95% CI 1.97-2.03). The IMR of nervous system anomaly was significantly higher in the youngest maternal age group (group I, 10-19 yr) with 3.63 per 10,000 live births (OR 2.0, 95% CI 1.97-2.03), compared to that in group III (0.32 per 10,000 live births). In fetal deaths related to birth defect, most FMRs by birth defects were highest in the youngest group, except for FMR by chromosomal abnormality which was significantly higher in group V compared to that in group III (OR 7.01, 95% CI, 2.09-23.52) (Table 5, Figure 2). Compared to FMR of group II, FMRs of chromosomal abnormality were significantly higher in group IV

and V (OR 5.00, 95% CI, 1.10-22.84 and OR 10.52, 95% CI 2.47-44.88, respectively). FMRs by total birth defects were significantly higher in group I and V, compared to that in group III, (OR 6.59, 95% CI 3.49-12.43 and OR 3.46, 95% CI 1.77-6.78, respectively). Individually, FMRs for anomalies of nervous system and cardiovascular system, and, other and unspecified anomalies were significantly higher in group I, compared to those in group III, (OR 15.04, 95% CI 3.59-62.96; OR 10, 95%CI 1.23-78.2, and OR 8.35, 95% CI 2.52-27.67, respectively)

Discussion

It is important to know severe birth defects which can lead fetal and infant deaths and its prevalence. Previously, the prevalence of birth defects in Korea in live births in 2005 and 2006 was reported to be approximately 2.9% [12], similar to those (2-3%) of other studies [1-3]. However, the other study reported the prevalence of birth defects in Korea in 2009 and 2010 as 5.8% [13]. Although there might be methodological limitation and variations, the prenatal and postnatal detection rates of birth defects in live births seems increasing. In this study, 22.8% of infant deaths of Korea were related to birth defects. IMR and FMR caused by birth defects between 2009 and 2015 were 6.84 per 10,000 live births and 13.47 per 10,000 total births, respectively.

The most common birth defect group related to infant deaths was anomaly of the circulatory system. However, the most common birth defect subtype was CDH. Despite advances in prenatal diagnosis and neonatal intensive care including extracorporeal membrane oxygenation and inhaled nitric oxide use, mortality rates due to CDH remain high, ranging from 50% to 70% with great variability

between centers [15-17]. The second most common birth defect in infant deaths related to birth defect was TOF. The 10-year survival rate of TOF has been reported to be approximately 95 % [18, 19]. When we consider the prevalence of TOF in live births in Korea with 4.1-4.2 per 10,000 live births [12, 13] and the IMR by TOF with 0.28 per 10,000 live births in this study, we can speculate that nationwide infant survival rates of TOF in Korea will be approximately 93.3%, which is similar to that in the other reports [18, 19].

As expected, when IMRs and FMRs caused by birth defects were compared according to maternal age group, IMRs and FMRs due to chromosomal abnormality were higher in older maternal age groups (IV and V) compared to those in group II or III. FMRs due to birth defects were significantly higher in groups I and V compared to those in group III (OR: 6.59, 95% CI: 3.49-12.43 and OR: 3.46, 95% CI: 1.77-6.78, respectively). FMR was much higher in group I. Especially, IMR and FMR due to anomalies of the nervous system were significantly higher in group I compared with those in group III, indicating higher prevalence of severe anomalies of nervous system in teenage pregnancies. In North America, fortification of flour and grain products became mandatory in 1998. Following folic acid fortification, prevalence of spina bifida birth in Canada fell by over 50% and that of other neural tube defects (NTDs) fell by approximately one-third [20]. In addition, the registry of 'European surveillance of congenital anomalies' has concluded that mandatory folic acid fortification is needed because the prevalence of NTDs has not decreased in Europe despite longstanding recommendations aiming at promoting periconceptional folic acid supplementation [21]. Results of Cochrane databases systematic review also showed a protective effect of daily folic acid supplementation in preventing NTDs compared to no intervention/placebo or vitamins and minerals without folic acid (risk ratio 0.31, 95% CI 0.17- 0.58); five studies; 6708 births; high

quality evidence) [22]. Teenage pregnancies are more likely unplanned and exposed to alcohol, drug, sexual abuse, and nutritional imbalance. When pregnancies are complicated by birth defects in young age, they might lead to TOP, more easily. This study demonstrated increasing trends of IMRs and FMRs due to birth defects in the youngest and oldest maternal age groups. However, high IMRs and FMRs due to birth defects in the youngest age group were more pronounced except for chromosomal abnormality. It is known that adolescent pregnancy is associated with higher risks of adverse neonatal outcomes, such as low birth weight, preterm delivery [23]. In regard to birth defects, gastroschisis has been shown to be higher in young mothers [24, 25]. However, there has been no other associations between young maternal age and any other birth defect, to our knowledge. Although it is unclear whether high IMRs and FMRs related to birth defects in the youngest maternal age group in this study are associated maternal age, or other social, nutritional, and environmental factors, further investigation might be needed in the future. In addition, mandatory folic acid fortification in Korea might help reduce nervous system anomalies because the youngest age group is less likely to take periconceptional folic acid supplementation and the overall prevalence of spina bifida in Korea shows increasing tendency [13].

In Europe, increasing trend of trisomy 13, 18, and 21 between 1990 and 2009 was reported [9]. In Korea, most of prenatal screening methods are available, such as the first trimester combined test, Quad screening, integrated, sequential test and cell-free DNA screening [26]. However, the legally acceptable pregnancy termination is very restrictive in Korea. The maternal and child health law only permits an abortion for one of the following reasons; if the pregnant woman or her spouse suffers from an eugenic or hereditary mental or physical disease specified by presidential decree, if the woman or her spouse suffers from a communicable disease specified

by presidential decree, if the pregnancy results from rape or incest or if continuation of the pregnancy is likely to jeopardize the mother's health. Therefore, it is almost impossible to estimate the proportions of TOP due to birth defects among fetal deaths. An international study has reported that the total mean prevalence of Down syndrome (still births, live births, and TOP) is increased from 13.1 to 18.2/10,000 births between 1993 and 2004 with increasing maternal age [27]. However, the total mean prevalence of Down syndrome births remains stable at 8.3/10,000 births, balanced by a great increase of TOP [27]. Maternal age at conception has increased in Korea, although there are race/ethnic specific variations in birth defects [28]. IMR and FMR by Down syndrome was 0.27 per 10,000 live births and 1.78 per 10,000 total births, respectively. When we assume the prevalence of Down syndrome in as 3.7-4.7 per 10,000 live births from the previous studies in Korea [12, 13], infant survival rate of Down syndrome can be estimated approximately 93.6%. Based on the increased prevalence of Down syndrome in the international study, according to increasing maternal age [27], we can expect that TOP due to Down syndrome may be also considerable in Korea.

The first limitation of this study is that death cause of fetal/infant deaths might be mostly made by clinician without autopsy. Although most autopsies performed in the Republic of Korea are forensic autopsies, the autopsy rates for total mortality and unusual death in Korea were reported as 2.4% and 18.1%, respectively, in 2015, which were very low [29, 30]. It could be related with the overwhelming majority of fetal losses due to unspecified nervous, cardiovascular, and other system. Because one or two disease codes are registered as the main code in death registry, multiple anomalies might have been included in one category. The second limitation of this study is that it does not show present prevalence of birth defects in live births. Therefore, it is necessary to establish a comprehensive surveillance system with periodic production of data and monitoring to have effective prevention and management of

birth defects. Lastly, this study did not include data on maternal nationality, paternal age, educational background, antenatal care, or parents' occupation due to high rates of missing values. However, this study is the first one that reports IMRs and FMRs caused by birth defects in Korea and different patterns according to maternal age group. Severe birth defects with high FMR were found to be more common in extreme maternal age groups (the youngest and the oldest). Except chromosomal abnormality, most severe anomalies, especially those of the nervous system and cardiovascular system, were more common in teenage pregnancies.

As maternal age at conception is getting increased in Korea and screening tools are developing, prevalence and prenatal diagnosis of chromosomal anomalies are likely to be increased. Multi-disciplinary cooperation among government, politician, clinicians, and non-governmental organization is urgent not only for increasing fertility rate, but also for increasing heathy pregnancies with effective prevention and management of birth defects, especially for extreme maternal age groups and for supporting complicated pregnancies. A mandatory folic acid fortification needs to be discussed and considered in Korea.

Author contributions

We confirm that all the authors have made substantive intellectual contributions to the paper; they understand their role in taking responsibility and being accountable for what is published. JCS conceptualized and reviewed the paper. HSK and DJK conceptualized the paper, gathered the results, analyzed the data and wrote the article. YHC, JHW, SKC, and IYP analyzed the data and reviewed the paper. YGP performed statistical analysis of the data.

Funding

This study was supported by Research Fund of Seoul St. Mary's Hospital, The Catholic University of Korea.

Conflict of Interest

All authors have no conflict of interest related with this article.

Details of ethics approval

We obtained approval from the institutional review board of Catholic University of Korea (KC17ZESI0409).

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Table 1. Demographic characteristics of total live births, total fetal deaths, total infant deaths, and fetal/infant deaths related with birth defect

Parameters	Total live births	Total fetal deaths	Total infant deaths	Infant deaths by birth defects	Fetal deaths by birth defects
	n=3,181,145	n=43,385	n=9563	n=2,176	n=4,343
Maternal age (yr)	31.9 ± 26.7	30.7 ± 6.2	31.6 ± 5.0	31.7 ± 4.9	21.2 ± 4.4
Gestational age (weeks)	38.6 ± 2.3	20.1 ± 5.8	32.2 ± 6.6	35.9 ± 4.4	31.8 ± 5.6
Birthweight (kg)	3.21 ± 0.48	0.69 ± 0.78	1.96 ± 1.15	2.47 ± 0.87	0.51 ± 0.5
Multiple birth n (%)	101,797 (3.2)	3,818 (8.8)	1492 (15.6)	196 (9)	200 (4.6)

Data are mean ± standard deviation or no. (%) unless otherwise specified.

Table 2. Korean prevalence of fetal deaths and infant deaths caused by birth defect groups in 2009-2015

Birth defects (ICD-10)	Total N. of fetal and infant deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10,000 live births and fetal deaths	N. of infant deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10,000 live births	N. of fetal deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10,000 total births
Nervous system (Q00-07)	970	14.88	3.01	136	6.25	0.43	834	19.20	2.59
Eye, ear, face and neck (Q10-18)	8	0.12	0.02	1	0.05	0.00	7	0.16	0.02
Circulatory system (Q20-28)	1605	24.62	4.98	1112	51.10	3.50	493	11.35	1.53
Respiratory system (Q30-34)	115	1.76	0.36	87	4.00	0.27	28	0.64	0.09
Cleft lip/ palate (Q35-37)	67	1.03	0.21	3	0.14	0.01	64	1.47	0.20
Digestive system (Q38-45)	203	3.11	0.63	169	7.77	0.53	34	0.78	0.11
Genital organs (Q50-56)	5	0.08	0.02	0	0.00	0.00	5	0.12	0.02
Urinary system (Q60-64)	213	3.27	0.66	54	2.48	0.17	159	3.66	0.49
Musculoskeletal system (Q65-79)	384	5.89	1.19	208	9.56	0.65	176	4.05	0.55
Other and unspecified (Q80-89)	1291	19.80	4.00	186	8.55	0.58	1105	25.44	3.43
Chromosomal abnormalities (Q90-99)	1658	25.43	5.14	220	10.11	0.69	1438	33.11	4.46
Total	6519	100.00	20.22	2176	100.00	2.64	4343	100.00	13.47

ICD, International classification of diseases, 10th revision.

Table 3. Prevalence of infant and fetal deaths caused by major chromosomal abnormalities in Korea, 2009-2015

Chromosomal birth defects	Total N. of cases caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 total births	N. of infant deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 live births	N. of fetal deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 total births
Down's syndrome	659	10.11	2.04	85	3.91	0.27	574	13.22	1.78
Trisomy 18	340	5.22	1.05	76	3.49	0.24	264	6.08	0.82
Trisomy 13	62	0.95	0.19	21	0.97	0.07	41	0.94	0.13
Kleinfelter's syndrome	33	0.51	0.10	0	0.00	0.00	33	0.76	0.10
Turner's syndrome	51	0.78	0.16	0	0.00	0.00	51	1.17	0.16
Other sex chromosome abnormalities	14	0.21	0.04	0	0.00	0.00	14	0.32	0.04
Triploidy	14	0.21	0.04	0	0.00	0.00	14	0.32	0.04
Wolff-Hirschorn syndrome	5	0.08	0.02	2	0.09	0.01	3	0.07	0.01
Cri-du-chat syndrome	5	0.08	0.02	2	0.09	0.01	3	0.07	0.01
Other chromosomal abnomalities	475	7.29	1.47	34	1.56	0.11	441	10.15	1.37
Total	1658	25.43	5.14	220	10.11	0.69	1438	33.11	4.46

Table 4. Comparison of infant mortality by birth defect according to maternal age group

	IMR								
Maternal age group Birth defects (ICD-10)	I (10-19 y)	OR (95% CI)	II (20-29 y)	OR (95% CI)	III (30-34 y)	IV (35-39 y)	OR (95% CI)	V (40-50 y)	OR (95% CI)
Nervous system (Q00-07)	3.63	**2 (1.97-2.03)**	0.42		0.32	0.52		1.21	
Eye, ear, face and neck (Q10-18)	0.00		0.00		0.01	0.00		0.00	
Circulatory system (Q20-28)	7.25		3.29		3.25	4.10		6.04	
Respiratory system (Q30-34)	0.00		0.23		0.24	0.32		1.21	
Cleft lip/ palate (Q35-37)	0.00		0.00		0.02	0.00		0.00	
Digestive system (Q38-45)	0.52		0.57		0.48	0.63		0.40	
Urinary system (Q60-64)	0.52		0.18		0.14	0.15		0.67	
Musculoskeletal system (Q65-79)	0.00		0.60		0.64	0.84		0.67	
Other and unspecified (Q80-89)	1.55		0.46		0.56	0.73		1.61	
Chromosomal abnormalities (Q90-99)	0.00		0.48		0.50	1.27		3.63	**2 (1.97-2.03)**
Total	13.47		6.22		6.16	8.56		15.44	

ICD, International classification of diseases, 10th revision; IMR, Infant mortality rate; OR, odd ratio; CI, confidence interval. IMRs by birth defects in group III were used as a reference for comparison with IMRs of other groups. Statistically significant values were presented.

Table 5. Comparison of fetal mortality by birth defect according to maternal age group

	FMR									
Maternal age group	I	OR	II	OR	III	OR	IV	OR	V	OR
Birth defects (ICD-10)	(10-19 y)	(95% CI)	(20-29 y)	(95% CI)	(30-34 y)	(95% CI)	(35-39 y)	OR (95% CI)	(40-50 y)	OR (95% CI)
Nervous system (Q00-07)	29.84	**15.04 (3.59-62.96)**	2.63	·	1.97		2.64	·	5.97	·
Eye, ear, face and neck (Q10-18)	0.45	·	0.03	·	0.01		0.02	·	0.13	·
Circulatory system (Q20-28)	9.95	**10 (1.23-78.20)**	1.48	·	1.34		1.83	·	1.43	·
Respiratory system (Q30-34)	0.45	·	0.12	·	0.06		0.09	·	0.00	·
Cleft lip/ palate (Q35-37)	0.00	·	0.27	·	0.18		0.17	·	0.13	·
Digestive system (Q38-45)	1.36	·	0.12	·	0.06		0.13	·	0.13	·
Genital organs (Q50-56)	0.51	·	0.01	·	0.02		0.02	·	0.00	·
Urinary system (Q60-64)	0.00	·	0.52	·	0.49		0.31	·	1.17	·
Musculoskeletal system (Q65-79)	0.90	·	0.64	·	0.49		0.50	·	0.26	·
Other and unspecified (Q80-89)	24.87	**8.35 (2.52-27.67)**	3.40	·	2.66		4.13	·	7.92	·
Chromosomal abnormalities (Q90-99)	4.07	·	1.87	·	3.39		10.11	·	20.64	**7.01 (2.09-23.52)**
Chromosomal abnormalities (Q90-99)*	4.07	·	1.87	·	3.39	·	10.11	**5 (1.10-22.84)**	20.64	**10.52 (2.47-44.88)**
Total	71.89	**6.59 (3.49-12.43)**	11.07	·	10.68		19.95	·	37.78	**3.46 (1.77-6.78)**

ICD, International classification of diseases, 10th revision; FMR, fetal mortality rate; OR, odd ratio; CI, confidence interval. FMRs by birth defects in group III were used as a reference for comparison with FMRs of other groups. *Comparison was performed between group II (reference) and the other groups. Statistically significant values were presented.

Figure 1. Infant mortality caused by birth defects, according to maternal age group.

Maternal age groups: ‘10-19 yr’ (I), ‘20-29 yr’ (II), ‘30-34 yr’ (III), ‘35-39 yr’ (IV), and ‘40-55 yr’ (V).

Figure 2. Fetal mortality caused by birth defects, according to maternal age group.

Maternal age groups: ‘10-19 yr’ (I), ‘20-29 yr’ (II), ‘30-34 yr’ (III), ‘35-39 yr’ (IV), and ‘40-55 yr’ (V).

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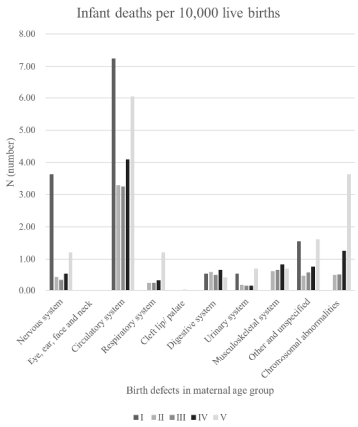

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Maternal age groups: '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).

338x190mm (300 x 300 DPI)

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Maternal age groups: '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).

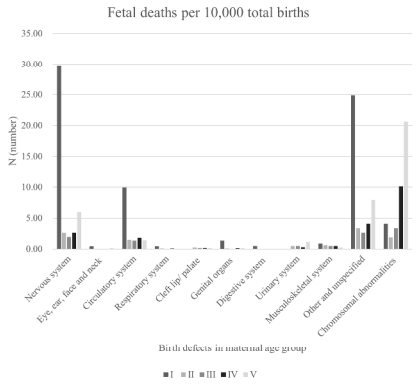

Figure 2. Fetal mortality caused by birth defects, according to maternal age group.
Maternal age groups: '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).

338x190mm (300 x 300 DPI)

Supplementary material.
Korean prevalence of fetal deaths and infant deaths caused by birth defect subtypes in 2009-2015

Birth defects (ICD-10)	N. of infant deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 livebirths	N. of fetal deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 total births
Nervous system (Q00-07)						
Anencephaly (Q00.0-00.2)	37	1.70	0.12	213	4.90	0.66
Encephalocele (Q01.0-01.9)	3	0.14	0.01	32	0.74	0.10
Congenital Hydrocephalus (Q03.0-03.9)	34	1.56	0.11	157	3.62	0.49
Holoprosencephaly (Q04.0-04.2)	14	0.64	0.04	46	1.06	0.14
Other brain anomaly (Q43-49)	36	1.65	0.11	131	3.02	0.41
Spina bifida (Q05.0-05.9)	8	0.37	0.03	28	0.64	0.09
Other spinal anomaly (Q68-69)	0	0.00	0.00	3	0.07	0.01
Arnold-Chiari malformation (Q70)	1	0.05	0.00	18	0.41	0.06
Other nervous system anomaly (Q78-79)	3	0.14	0.01	206	4.74	0.64
Eye, ear, face and neck (Q10-18)	1	0.05	0.00	7	0.16	0.02
Circulatory system (Q20-28)						
Truncus arteriosus (Q20.0)	9	0.41	0.03	1	0.02	0.00
Double outlet right ventricle	66	3.03	0.21	7	0.16	0.02
Transposition of great arteries (Q20.1-20.3)	72	3.31	0.23	0	0.00	0.00
Double inlet ventricle (Q20.4)	58	2.67	0.18	1	0.02	0.00
Discordant atrioventricular connection (Q20.5)	2	0.09	0.01	1	0.02	0.00
Isomerism of atrial appendages (Q20.6)	3	0.14	0.01	1	0.02	0.00
Ventricular septal defect (Q21.0)	50	2.30	0.16	20	0.46	0.06
Atrial septal defect (Q21.1)	20	0.92	0.06	2	0.05	0.01
Atrioventricular septal defect (Q21.2)	72	3.31	0.23	4	0.09	0.01
Tetralogy of Fallot (Q21.3)	88	4.04	0.28	21	0.48	0.07
Other malformations of cardiac septa (Q21.4, 21.8, 21.9)	6	0.28	0.02	10	0.23	0.03
Pulmonary valve atresia/stenosis (Q22.0-22.1)	52	2.39	0.16	1	0.02	0.00
Congenital tricuspid stenosis (Q22.4)	5	0.23	0.02	1	0.02	0.00
Ebstein's anomaly (Q22.5)	23	1.06	0.07	7	0.16	0.02
Hypoplastic right heart syndrome (Q22.6)	1	0.05	0.00	1	0.02	0.00
Other malformations of tricuspid valve (Q22.8, 22.9)	3	0.14	0.01	4	0.09	0.01
Aortic valve stenosis/insufficiency (Q23.0, 23.1)	9	0.41	0.03	3	0.07	0.01

Mitral valve stenosis/insufficiency (Q23.2, 23.3)	8	0.37	0.03	0	0.00	0.00
Hypoplastic left heart syndrome (Q23.4)	86	3.95	0.27	7	0.16	0.02
Dextrocardia (Q 24.0)	0	0.00	0.00	3	0.07	0.01
Cor triatriaum (Q 24.2)	2	0.09	0.01	0	0.00	0.00
Subaortic stenosis (Q 24.4)	2	0.09	0.01	0	0.00	0.00
Malformation of coronary vessels (Q24.5-24.6)	6	0.28	0.02	0	0.00	0.00
Other heart malformation (Q24.2, 24.4-24.6)	88	4.04	0.28	50	1.15	0.16
Unspecified heart malformation (Q24.9)	75	3.45	0.24	299	6.88	0.93
Patent ductus arteriosus (Q25.0)*	87	4.00	0.27	0	0.00	0.00
Coarctation/atresia/stenosis of aorta (Q25.1-25.3)	55	2.53	0.17	0	0.00	0.00
Other malformations of aorta (Q25.4)	18	0.83	0.06	4	0.09	0.01
Pulmonary artery atresia/stenosis (Q25.5, 25.6)	22	1.01	0.07	2	0.05	0.01
Total anomalous pulmonary venous connection (Q26.2)	83	3.81	0.26	0	0.00	0.00
Partial anomalous pulmonary venous connection (Q26.3)	3	0.14	0.01	1	0.02	0.00
Peripheral arteriovenous malformation (Q27.3, 27.9, 27.9)	1	0.05	0.00	4	0.09	0.01
Malformations of cerebral vessels (Q 28.2, 28.3)	6	0.28	0.02	4	0.09	0.01
Other malformations of circulatory system (Q20.8, 20.9, 22.3, 25.7-26.1, 26.4, 27.0, 26.8, 28,8, 28.9)	31	1.42	0.10	34	0.78	0.11
Respiratory system (Q30-34)						
Other malformations of larynx, bronchus, trachea (Q31.0-32.4)	34	1.56	0.11	3	0.07	0.01
Congenital cystic lung (Q33.0)	5	0.23	0.02	5	0.12	0.02
Other malformation of lung (Q33.1-33.9)	42	1.93	0.13	16	0.37	0.05
Other malformations of respiratory system (Q34)	6	0.28	0.02	4	0.09	0.01
Cleft lip/palate (Q35-37)	3	0.14	0.01	64	1.47	0.20
Digestive system (Q38-45)						
Other malformation of mouths (Q38.5)	0	0.00	0.00	1	0.02	0.00
Esophageal atresia/stenosis (Q39.0-39.2)	34	1.56	0.11	6	0.14	0.02
Malformation of upper elimentary tract (Q40.0-40.9)	3	0.14	0.01	3	0.07	0.01
Duodenal atresia/stenosis (Q41.0)	3	0.14	0.01	7	0.16	0.02
Small intestine atresia/stenosis (Q41.1-41.9)	22	1.01	0.07	1	0.02	0.00
Anorectal atresia/stenosis (Q42.0-42.3)	2	0.09	0.01	2	0.05	0.01
Congenital megacolon (Q43.1)	44	2.02	0.14	0	0.00	0.00
Malrotation of colon (Q43.3)	9	0.41	0.03	0	0.00	0.00
Persistent cloaca (Q43.7)	1	0.05	0.00	2	0.05	0.01

Other intestinal and bile duct malformation (Q43.8-44.3)	42	1.93	0.13	6	0.14	0.02
Liver malformation (Q44.7)	4	0.18	0.01	0	0.00	0.00
Other malformation of digestive system (Q 42.8, 43.0, 45.8, 45.9)	5	0.23	0.02	6	0.14	0.02
Genital organs (Q50-56)	0	0.00	0.00	5	0.12	0.02
Urinary system (Q60-64)						
Renal agenesis (Q60.0-60.6)	22	1.01	0.07	44	1.01	0.14
Autosomal recessive polycystic kidney (Q61.1)	10	0.46	0.03	6	0.14	0.02
Unspecified polycystic kidney (Q61.3)	6	0.28	0.02	23	0.53	0.07
Renal dysplasia (Q61.4)	6	0.28	0.02	30	0.69	0.09
Cystic kidney (Q61.0, Q61.5-61.9)	1	0.05	0.00	3	0.07	0.01
Congenital hydronephrosis (Q62.0-62.8)	2	0.09	0.01	14	0.32	0.04
Other renal anomaly (Q63.0, 63.2, 63.8, 63.9)	3	0.14	0.01	30	0.69	0.09
Posterior urethral valve (Q64.2)	3	0.14	0.01	3	0.07	0.01
Congenital absence of bladder and urethra (Q64.5-64.9)	1	0.05	0.00	6	0.14	0.02
Musculoskeletal system (Q65-79)						
Club foot-talipes equinovarus (66.0)	0	0.00	0.00	1	0.02	0.00
Other congenital feet deformities (Q66.1-66.9)	0	0.00	0.00	4	0.09	0.01
Congenital deformities of skull, face, and jaw (Q67.0-67.4)	0	0.00	0.00	2	0.05	0.01
Pectus carinatum (Q67.6)	2	0.09	0.01	0	0.00	0.00
Other congenital musculoskeletal deformities (Q68.0-Q70.9)	0	0.00	0.00	12	0.28	0.04
Total limb reduction defects (Q71.0-71.9, Q72.0-72.9, Q73.0-73.8)	0	0.00	0.00	8	0.18	0.02
Other malformation of limbs and pelvic girdle (Q74.0-Q74.2, 74.8)	3	0.14	0.01	19	0.44	0.06
Arthrogryposis multiplex congenita (Q74.3)	4	0.18	0.01	1	0.02	0.00
Craniosynostosis (Q75.0)	6	0.28	0.02	0	0.00	0.00
Malformations of skul and face bones (Q75.1-75.9)	6	0.28	0.02	7	0.16	0.02
Klippel-Feil syndrome (Q76.1)	2	0.09	0.01	0	0.00	0.00
Malformations of spine and bony thorax (Q76.2-76.9)	2	0.09	0.01	7	0.16	0.02
Achondrogenesis/Hypochondrogenesis (Q77.0)	2	0.09	0.01	1	0.02	0.00
Thanatophoric dysplasia (Q77.1)	7	0.32	0.02	20	0.46	0.06
Asphyxiating thoracic dysplasia (Q77.2)	1	0.05	0.00	3	0.07	0.01
Achondroplasia/hypochondroplasia (Q77.4)	3	0.14	0.01	9	0.21	0.03
Osteogenesis imperfecta (Q78.0)	2	0.09	0.01	6	0.14	0.02

Other osteochondrodysplasia (Q77.8, 78.8, 78.9)	2	0.09	0.01	4	0.09	0.01
Diaphragmatic hernia (Q79.0)	138	6.34	0.43	22	0.51	0.07
Other malformations of diaphragm (Q79.1)	6	0.28	0.02	1	0.02	0.00
Omphalocele (Q79.2)	10	0.46	0.03	15	0.35	0.05
Gastroschisis (Q79.3)	8	0.37	0.03	12	0.28	0.04
Prune belly syndrome (Q79.4)	0	0.00	0.00	3	0.07	0.01
Other musculoskeletal anomaly (Q79.8, 79.9)	4	0.18	0.01	19	0.44	0.06
Other and unspecified (Q80-89)	186	8.55	0.58	1105	25.44	3.43
Chromosomal abnormalities (Q90-99)	220	10.11	0.69	1438	33.11	4.46

*Patent ductus arteriosus cases included 81 cases whose birthweight was less than 2,500 g.

N, number.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4,5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not applicable

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7,8,9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(*b*) Report category boundaries when continuous variables were categorized	7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

A national cohort study evaluating infant and fetal mortality caused by birth defects in Korea

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017963.R2
Article Type:	Research
Date Submitted by the Author:	04-Oct-2017
Complete List of Authors:	Ko, Hyun Sun; Catholic University of Korea School of Medicine, Kim, Dong Joo; Catholic University of Korea, obstetrics and gynecology; St. Mary's women's hospital, Obstetrics and gynecology Chung, Yoohyun; Catholic University of Korea School of Medicine Wie, Jeong Ha; Catholic University of Korea School of Medicine Choi, Sae Kyung; Catholic University of Korea School of Medicine Park, In Yarg; Catholic University of Korea School of Medicine Park, Yong Gyu; Catholic University of Korea School of Medicine Shin, Jong Chul; Catholic University of Korea School of Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology, Health policy, Public health
Keywords:	birth defect, infant, fetal, mortality, maternal age

A national cohort study evaluating infant and fetal mortality caused by birth defects in Korea

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Key words; birth defect, infant death, fetal death, maternal age

Running title: Infant and fetal mortality caused by birth defects in Korea

Tweetable abstract: Severe anomalies except chromosomal abnormality were the most prevalent in teenage pregnancies.

Abstract

Objective: To analyze the prevalence of fetal and infant deaths due to birth defects in Korea and those trends according to maternal age.

Design: Retrospective national cohort study

Setting: Database in Korean vital Statistics, between 2009 and 2015.

Participants: 2,176 infant deaths and 4,343 fetal deaths caused by birth defects, among 3,181,145 total live births and 43,385 fetal deaths during study periods

Methods: Infant and fetal mortality rates (IMRs and FMRs) by birth defects, from deaths caused by birth defects, were analyzed. Those were compared, according to maternal age groups; '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).

Main Outcome Measures: IMRs and FMRs by birth defects and comparison according to maternal age group.

Results: IMRs and FMRs by birth defects were 6.84 per 10,000 live births, and 13.47 per 10,000 total births. The most common causes of infant deaths and fetal deaths by birth defect were anomaly of circulatory system (51.1%, IMR 3.5) and chromosomal abnormality (33.1%, FMR 4.46), respectively. Among groups by maternal age, FMRs by birth defects were significantly higher in group I and V, compared to it in group III, (Odd ratio (OR) 6.59, 95% CI 3.49-12.43 and 3.46, 95% CI 1.77-6.78, respectively). IMR and FMR by nervous system anomaly were significantly higher in group I, with 3.63 (OR 2.0, 95% CI 1.97-2.03) and 29.84 (OR15.04, 95% CI 3.59-62.96), compared to 0.32 and 1.97 in group III.

Conclusion: FMRs by birth defects were the highest in extreme maternal age groups. Severe anomalies except chromosomal abnormality were the most prevalent in teenage pregnancies.

Strengths and limitations of this study

- This study is the first one that reports infant and fetal mortalities caused by birth defects in Korea, from the national vital statistics.
- This study compared the infant and fetal mortalities caused by birth defects, according to maternal age group, which showed higher prevalence of them in teenage pregnancies.
- The limitation of this study is that causes of fetal/infant deaths were mostly diagnosed clinically without autopsy and there is no available data about spontaneous or induced abortion in fetal deaths.

- The limitation of this study is that it does not show present prevalence of birth defects in live births.

Introduction

Birth defects (structural abnormalities, sensory changes, chromosomal abnormalities, metabolic abnormalities, and neurodevelopmental defects) are presented in approximately 2-3% of all births [1-3]. Severe birth defects account for 20-25% of perinatal mortality and they are leading causes of infant mortality, abortion, and stillbirth [2-5]. During the last decade, screening tests and ultrasonography during pregnancy have been developed to detect birth defects. However, etiologies of 60-70% of birth defects remain unknown.

In developed countries, birth defects surveillance systems have been developed to collect data on major structural birth defects and chromosomal abnormalities [6-8]. European registry reported that total and live birth prevalence of trisomies 21, 18 and 13 were increased between 1990 and 2009, and those were mainly associated with increasing maternal age [9].

While the number of live births in Korea has been decreased, the number of maternal age has been increased [10, 11]. The prevalence of birth defects in Korean live births has been reported before, using the data based on the National Health Insurance Corporation and medical institutes across the country [12, 13]. However, it is important to include stillbirths in addition to live births to account for all pregnancies within birth defects. Although it is hard to include spontaneous abortion in the early stage of pregnancy, the investigation

of fetal death related with birth defect can be useful for estimating the prevalence of birth defects. In addition, investigation of infant death related to birth defect can be valuable information for counseling parents, antenatally and postnatally.

The aim of this study was to analyze the prevalence of fetal and infant deaths associated with birth defects, which are fetal/infant mortality rates (FMR/IMR) by birth defect, and evaluate changes of those prevalence rates, according to maternal age.

Materials and Methods

This national cohort study was conducted by utilizing deidentified data about fetal deaths, infant deaths, and live births between 2009 and 2015 from 'Korean Vital Statistics' of the Korean Statistical Information Service [10]. Korean Vital Statistics is a nationwide database developed to understand birth, death, marriage, and divorce in Korea. Data from Korean Vital Statistics are released monthly and annually via a press release, on website (http://kosis.kr), and in online publications, such as 'Annual Report on Vital Statistics.' Since 2007, surveys and statistical analysis methods for infant and maternal death have been revised and complemented [14] to develop into a method for calculating more concrete, accurate numbers for fetal, infant, and maternal mortality rates in Korea. In summary, revision and supplementation of the statistics for fetal, infant and maternal death have been performed and validated by combination of official death registry data for vital statistics, survey data of public health center or medical institution, medical insurance claims database of the National Health Insurance Corporation on medical institutes across the country, and cremation reports data. Because national data about fetal death has been included since 2009, study cohort for this study was made by data between 2009 and 2015. However, data did not include information whether the cause of death was proven by autopsy. From fetal

and infant deaths data, fetal and infant death recorded as ‘a death caused by birth defect’ were included in fetal and infant deaths associated with birth defect. Fetal death was defined as intrauterine fetal death occurring after 16 weeks of gestational age and before the start of delivery or those occurring during labor. Infant death was defined as a death occurring within the first year of life.

Birth defects were categorized by birth defect group (the system affected) and subtype (individual disease) according to the 10th Revision of the International Classification of Diseases (ICD-10) and were investigated by including major groups of birth defects managed by EUROCAT, ICBDSR, and the National Birth Defects Prevention Network (NBDPN). Deaths caused by disease code ‘Q’ representing congenital disease were defined as fetal and infant deaths related to birth defect. According to the above standards, 2,176 infant deaths and 4,343 fetal deaths were caused by birth defect. This study calculated IMR by birth defects by dividing the number of infant deaths related to birth defects by the total number of live births. It was presented as the number per 10,000 live births as a standard. FMR by birth defects was calculated by dividing the number of fetal deaths related with birth defect by the total number of live births and fetal deaths, which presented as the number per 10,000 total births. Maternal age groups were divided to the following five groups: ‘10-19 yr’ (I), ‘20-29 yr’ (II), ‘30-34 yr’ (III), ‘35-39 yr’ (IV), and ‘40-55 yr’ (V). IMRs and FMRs by birth defects in group III were used as control for comparison with IMRs/FMRs of other groups. For chromosomal abnormalities, comparison was also performed between group II and the other groups.

Statistical analysis

Statistical calculations were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA), including means, proportions, odd ratio (OR), and 95% confidence intervals (CIs). Chi-square tests were performed to compare proportions of independent variables and t-tests were performed to compare means. One decimal place was marked up in the presentation of maternal ages and gestational ages. Statistical significance was considered at $P < 0.05$ or if the 95% CI of OR did not include 1.

Ethics statement

The study protocol was approved by the institutional review board of Catholic University of Korea (KC17ZESI0409). Informed consent was waived by the board.

Results

Baseline characteristics

Total numbers of live births and fetal deaths in Korea from 2009 to 2015 were 3,181,145 and 43,385, respectively. Among 9,563 infant deaths during the 7 years, the number of infant deaths related to birth defect was 2,176, accounting for 22.8% of all infant deaths. The number of fetal deaths related to birth defects was 4,343, accounting for 10.0% of all fetal deaths. Baseline demographic characteristics are summarized in Table 1.

IMRs, by birth defect groups and subtypes

IMR by total birth defects was 6.84 per 10,000 live births (Table 2). Anomaly of the circulatory system was the most common cause of infant deaths related to birth defect, accounting for 51.1% of all infant deaths. Its IMR was 3.5 per 10,000 live births. The next most common defects in infant deaths were chromosomal abnormality (0.69 per 10,000 live births, 10.1%) and musculoskeletal system anomalies (0.65 per 10,000 live births, 9.6%). Among subtypes of birth defects, congenital diaphragmatic hernia (CDH) showed the highest IMR at 0.43 per 10,000 live births (supplementary material). Among specified anomalies, lethal birth defects with the next highest IMRs were Tetralogy of Fallot (TOF) and hypoplastic left heart syndrome (HLHS) (with IMRs of 0.28 and 0.27 per 10,000

live births, respectively). Among chromosomal abnormalities, Down syndrome was the most common chromosomal abnormality with IMR of 0.27 per 10,000 live births (Table 3).

FMRs by birth defect groups and subtypes

FMR by total birth defects was 13.47 per 10,000 total births (live births plus stillbirths) (Table 2). The most common birth defect by group was chromosomal abnormality, accounting for 33.1% of fetal deaths related to birth defect, and its FMR was 4.46 per 10,000 total births. The most common birth defect subtype in fetal deaths was Down syndrome with FMR of 1.78 per 10,000 total births, and followed by other chromosomal abnormality, unspecified congenital heart malformation, and Edward syndrome, with FMR of 1.36, 0.93 and 0.82 per 10,000 total births, respectively (Table 3 and supplementary material).

IMRs and FMRs by birth defect groups, according to the maternal age group

In the analysis according to maternal age group, 2,529 live births, 113 fetal deaths not related to birth defects, and 12 fetal deaths related to birth defects were excluded due to missing values of maternal age. In infant deaths related to birth defect, anomaly of the circulatory system was most common in all age groups (Table 4, Figure 1). IMRs of chromosomal abnormality seemed to be increased in groups IV and V compared to that in group III. However, statistically significant difference was only observed between group V and group III (OR 2.00 95% CI 1.97-2.03). The IMR of nervous system anomaly was significantly higher in the youngest maternal

age group (group I, 10-19 yr) with 3.63 per 10,000 live births (OR 2.0, 95% CI 1.97-2.03), compared to that in group III (0.32 per 10,000 live births). In fetal deaths related to birth defect, most FMRs by birth defects were highest in the youngest group, except for FMR by chromosomal abnormality which was significantly higher in group V compared to that in group III (OR 7.01, 95% CI, 2.09-23.52) (Table 5, Figure 2). Compared to FMR of group II, FMRs of chromosomal abnormality were significantly higher in group IV and V (OR 5.00, 95% CI, 1.10-22.84 and OR 10.52, 95% CI 2.47-44.88, respectively). FMRs by total birth defects were significantly higher in group I and V, compared to that in group III, (OR 6.59, 95% CI 3.49-12.43 and OR 3.46, 95% CI 1.77-6.78, respectively). Individually, FMRs for anomalies of nervous system and cardiovascular system, and, other and unspecified anomalies were significantly higher in group I, compared to those in group III, (OR 15.04, 95% CI 3.59-62.96; OR 10, 95%CI 1.23-78.2, and OR 8.35, 95% CI 2.52-27.67, respectively)

Discussion

It is important to know the types of severe birth defects which can lead fetal and infant deaths and their prevalence. Previously, the prevalence of birth defects in Korea in live births in 2005 and 2006 was reported to be approximately 2.9% [12], similar to those (2-3%) of other studies [1-3]. However, the other study reported the prevalence of birth defects in Korea in 2009 and 2010 as 5.8% [13]. Although there might be methodological limitation and variations, the prenatal and postnatal detection rates of birth defects in live

births seems increasing. In this study, 22.8% of infant deaths of Korea were related to birth defects. IMR and FMR caused by birth defects between 2009 and 2015 were 6.84 per 10,000 live births and 13.47 per 10,000 total births, respectively.

The most common birth defect group related to infant deaths was anomaly of the circulatory system. However, the most common birth defect subtype was CDH. Despite advances in prenatal diagnosis and neonatal intensive care including extracorporeal membrane oxygenation and inhaled nitric oxide use, mortality rates due to CDH remain high, ranging from 50% to 70% with great variability between centers [15-17]. The second most common birth defect in infant deaths related to birth defect was TOF. The 10-year survival rate of TOF has been reported to be approximately 95 % [18, 19]. When we consider the prevalence of TOF in live births in Korea with 4.1-4.2 per 10,000 live births [12, 13] and the IMR by TOF with 0.28 per 10,000 live births in this study, we can speculate that nationwide infant survival rates of TOF in Korea will be approximately 93.3%, which is similar to survival rates in the other reports [18, 19].

As expected, when IMRs and FMRs caused by birth defects were compared according to maternal age group, IMRs and FMRs due to chromosomal abnormality were higher in older maternal age groups (IV and V) compared to those in group II or III. FMRs due to birth defects were significantly higher in groups I and V compared to those in group III (OR: 6.59, 95% CI: 3.49-12.43 and OR: 3.46, 95% CI: 1.77-6.78, respectively). FMR was much higher in group I. Especially, IMR and FMR due to anomalies of the nervous system were significantly higher in group I compared with those in group III, indicating higher prevalence of severe anomalies of nervous system in teenage pregnancies. In North America, fortification of flour and grain products became mandatory in 1998.

Following folic acid fortification, prevalence of spina bifida birth in Canada fell by over 50% and that of other neural tube defects (NTDs) fell by approximately one-third [20]. In addition, the registry of 'European surveillance of congenital anomalies' has concluded that mandatory folic acid fortification is needed because the prevalence of NTDs has not decreased in Europe despite longstanding recommendations aiming at promoting periconceptional folic acid supplementation [21]. Results of Cochrane databases systematic review also showed a protective effect of daily folic acid supplementation in preventing NTDs compared to no intervention/placebo or vitamins and minerals without folic acid (risk ratio 0.31, 95% CI 0.17- 0.58); five studies; 6708 births; high quality evidence) [22]. Teenage pregnancies are more likely unplanned and exposed to alcohol, drug, sexual abuse, and nutritional imbalance. When pregnancies are complicated by birth defects in young age, they might be resulted in TOP, more easily. This study demonstrated increasing trends of IMRs and FMRs due to birth defects in the youngest and oldest maternal age groups. However, high IMRs and FMRs due to birth defects in the youngest age group were more pronounced except for chromosomal abnormality. It is known that adolescent pregnancy is associated with higher risks of adverse neonatal outcomes, such as low birth weight, preterm delivery [23]. In regard to birth defects, gastroschisis has been shown to be higher in young mothers [24, 25]. However, there has been no other associations between young maternal age and any other birth defect, to our knowledge. Although it is unclear whether high IMRs and FMRs related to birth defects in the youngest maternal age group in this study are associated maternal age, or other social, nutritional, and environmental factors, further investigation might be needed in the future. In addition, mandatory folic acid fortification in Korea might help reduce nervous system anomalies because the youngest age group is less likely to take periconceptional folic acid supplementation and the overall prevalence of spina bifida in Korea shows increasing tendency [13].

In Europe, increasing trend of trisomy 13, 18, and 21 between 1990 and 2009 was reported [9]. In Korea, most of prenatal screening methods are available, such as the first trimester combined test, Quad screening, integrated, sequential test and cell-free DNA screening [26]. However, the legally acceptable pregnancy termination is very restrictive in Korea. The maternal and child health law only permits an abortion for one of the following reasons; if the pregnant woman or her spouse suffers from an eugenic or hereditary mental or physical disease specified by presidential decree, if the woman or her spouse suffers from a communicable disease specified by presidential decree, if the pregnancy results from rape or incest or if continuation of the pregnancy is likely to jeopardize the mother's health. Therefore, it is almost impossible to estimate the proportions of TOP due to birth defects among fetal deaths. An international study has reported that the total mean prevalence of Down syndrome (in stillbirths, live births, and TOP) is increased from 13.1 to 18.2/10,000 births between 1993 and 2004 with increasing maternal age [27]. However, the total mean prevalence of Down syndrome live births remains stable at 8.3/10,000 births, balanced by a great increase of TOP [27]. Maternal age at conception has been increased in Korea, although there are race/ethnic specific variations in birth defects [28]. IMR and FMR by Down syndrome were 0.27 per 10,000 live births and 1.78 per 10,000 total births, respectively. When we assume the prevalence of Down syndrome in as 3.7-4.7 per 10,000 live births from the previous studies in Korea [12, 13], infant survival rate of Down syndrome can be estimated approximately 93.6%. Based on the increased prevalence of Down syndrome in the international study, according to increasing maternal age [27], we can expect that TOP due to Down syndrome may be also considerable in Korea.

The first limitation of this study is that death cause of fetal/infant deaths might be mostly made by clinician without autopsy. Although most autopsies performed in the Republic of Korea are forensic autopsies, the autopsy rates for total mortality and unusual death in

Korea were reported as 2.4% and 18.1%, respectively, in 2015, which were very low [29, 30]. It could be related with the overwhelming majority of fetal losses due to unspecified nervous, cardiovascular, and other system. Because one or two disease codes are registered as the main code in death registry, multiple anomalies might have been included in one category. The second limitation of this study is that it does not show present prevalence of birth defects in live births. Therefore, it is necessary to establish a comprehensive surveillance system with periodic production of data and monitoring to have effective prevention and management of birth defects. Lastly, this study did not include data on maternal nationality, paternal age, educational background, antenatal care, or parents' occupation due to high rates of missing values. However, this study is the first one that reports IMRs and FMRs caused by birth defects in Korea and different patterns according to maternal age group. Severe birth defects with high FMR were found to be more common in extreme maternal age groups (the youngest and the oldest). Except chromosomal abnormality, most severe anomalies, especially those of the nervous system and cardiovascular system, were more common in teenage pregnancies.

As maternal age at conception is getting increased in Korea and screening tools are developing, prevalence and prenatal diagnosis of chromosomal abnormalities are likely to be increased. Multi-disciplinary cooperation among government, politician, clinicians, and non-governmental organization is urgent not only for increasing fertility rate, but also for increasing heathy pregnancies with effective prevention and management of birth defects, especially for extreme maternal age groups and for supporting complicated pregnancies. A mandatory folic acid fortification needs to be discussed and considered in Korea.

Author contributions

We confirm that all the authors have made substantive intellectual contributions to the paper; they understand their role in taking responsibility and being accountable for what is published. JCS conceptualized and reviewed the paper. HSK and DJK conceptualized the paper, gathered the results, analyzed the data and wrote the article. YHC, JHW, SKC, and IYP analyzed the data and reviewed the paper. YGP performed statistical analysis of the data.

Funding

This study was supported by Research Fund of Seoul St. Mary's Hospital, The Catholic University of Korea.

Conflict of Interest

None declared.

Details of ethics approval

We obtained approval from the institutional review board of Catholic University of Korea (KC17ZESI0409).

Data sharing statement

There is no data sharing.

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Table 1. Demographic characteristics of total live births, total fetal deaths, total infant deaths, and fetal/infant deaths related with birth defect

Parameters	Total live births	Total fetal deaths	Total infant deaths	Infant deaths by birth defects	Fetal deaths by birth defects
	n=3,181,145	n=43,385	n=9563	n=2,176	n=4,343
Maternal age (yr)	31.9 ± 26.7	30.7 ± 6.2	31.6 ± 5.0	31.7 ± 4.9	21.2 ± 4.4
Gestational age (weeks)	38.6 ± 2.3	20.1 ± 5.8	32.2 ± 6.6	35.9 ± 4.4	31.8 ± 5.6
Birthweight (kg)	3.21 ± 0.48	0.69 ± 0.78	1.96 ± 1.15	2.47 ± 0.87	0.51 ± 0.5
Multiple birth n (%)	101,797 (3.2)	3,818 (8.8)	1492 (15.6)	196 (9)	200 (4.6)

Data are mean ± standard deviation or no. (%) unless otherwise specified.

Table 2. Korean prevalence of fetal deaths and infant deaths caused by birth defect groups in 2009-2015

Birth defects (ICD-10)	Total N. of fetal and infant deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10,000 live births and fetal deaths	N. of infant deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10,000 live births	N. of fetal deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10,000 total births
Nervous system (Q00-07)	970	14.88	3.01	136	6.25	0.43	834	19.20	2.59
Eye, ear, face and neck (Q10-18)	8	0.12	0.02	1	0.05	0.00	7	0.16	0.02
Circulatory system (Q20-28)	1605	24.62	4.98	1112	51.10	3.50	493	11.35	1.53
Respiratory system (Q30-34)	115	1.76	0.36	87	4.00	0.27	28	0.64	0.09
Cleft lip/ palate (Q35-37)	67	1.03	0.21	3	0.14	0.01	64	1.47	0.20
Digestive system (Q38-45)	203	3.11	0.63	169	7.77	0.53	34	0.78	0.11
Genital organs (Q50-56)	5	0.08	0.02	0	0.00	0.00	5	0.12	0.02
Urinary system (Q60-64)	213	3.27	0.66	54	2.48	0.17	159	3.66	0.49
Musculoskeletal system (Q65-79)	384	5.89	1.19	208	9.56	0.65	176	4.05	0.55
Other and unspecified (Q80-89)	1291	19.80	4.00	186	8.55	0.58	1105	25.44	3.43
Chromosomal abnormalities (Q90-99)	1658	25.43	5.14	220	10.11	0.69	1438	33.11	4.46
Total	6519	100.00	20.22	2176	100.00	2.64	4343	100.00	13.47

ICD, International classification of diseases, 10th revision.

Table 3. Prevalence of infant and fetal deaths caused by major chromosomal abnormalities in Korea, 2009-2015

Chromosomal birth defects	Total N. of cases caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 total births	N. of infant deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 live births	N. of fetal deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 total births
Down's syndrome	659	10.11	2.04	85	3.91	0.27	574	13.22	1.78
Trisomy 18	340	5.22	1.05	76	3.49	0.24	264	6.08	0.82
Trisomy 13	62	0.95	0.19	21	0.97	0.07	41	0.94	0.13
Kleinfelter's syndrome	33	0.51	0.10	0	0.00	0.00	33	0.76	0.10
Turner's syndrome	51	0.78	0.16	0	0.00	0.00	51	1.17	0.16
Other sex chromosome abnormalities	14	0.21	0.04	0	0.00	0.00	14	0.32	0.04
Triploidy	14	0.21	0.04	0	0.00	0.00	14	0.32	0.04
Wolff-Hirschorn syndrome	5	0.08	0.02	2	0.09	0.01	3	0.07	0.01
Cri-du-chat syndrome	5	0.08	0.02	2	0.09	0.01	3	0.07	0.01
Other chromosomal abnomalities	475	7.29	1.47	34	1.56	0.11	441	10.15	1.37
Total	1658	25.43	5.14	220	10.11	0.69	1438	33.11	4.46

Table 4. Comparison of infant mortality by birth defect according to maternal age group

	IMR								
Maternal age group Birth defects (ICD-10)	I (10-19 y)	OR (95% CI)	II (20-29 y)	OR (95% CI)	III (30-34 y)	IV (35-39 y)	OR (95% CI)	V (40-50 y)	OR (95% CI)
Nervous system (Q00-07)	3.63	**2 (1.97-2.03)**	0.42		0.32	0.52		1.21	
Eye, ear, face and neck (Q10-18)	0.00		0.00		0.01	0.00		0.00	
Circulatory system (Q20-28)	7.25		3.29		3.25	4.10		6.04	
Respiratory system (Q30-34)	0.00		0.23		0.24	0.32		1.21	
Cleft lip/ palate (Q35-37)	0.00		0.00		0.02	0.00		0.00	
Digestive system (Q38-45)	0.52		0.57		0.48	0.63		0.40	
Urinary system (Q60-64)	0.52		0.18		0.14	0.15		0.67	
Musculoskeletal system (Q65-79)	0.00		0.60		0.64	0.84		0.67	
Other and unspecified (Q80-89)	1.55		0.46		0.56	0.73		1.61	
Chromosomal abnormalities (Q90-99)	0.00		0.48		0.50	1.27		3.63	**2 (1.97-2.03)**
Total	13.47		6.22		6.16	8.56		15.44	

ICD, International classification of diseases, 10th revision; IMR, Infant mortality rate; OR, odd ratio; CI, confidence interval. IMRs by birth defects in group III were used as a reference for comparison with IMRs of other groups. Statistically significant values were presented.

Table 5. Comparison of fetal mortality by birth defect according to maternal age group

	FMR									
Maternal age group	I	OR	II	OR	III	OR	IV	OR	V	OR
Birth defects (ICD-10)	(10-19 y)	(95% CI)	(20-29 y)	(95% CI)	(30-34 y)	(95% CI)	(35-39 y)	OR (95% CI)	(40-50 y)	OR (95% CI)
Nervous system (Q00-07)	29.84	**15.04 (3.59-62.96)**	2.63	·	1.97		2.64	·	5.97	·
Eye, ear, face and neck (Q10-18)	0.45	·	0.03	·	0.01		0.02	·	0.13	·
Circulatory system (Q20-28)	9.95	**10 (1.23-78.20)**	1.48	·	1.34		1.83	·	1.43	·
Respiratory system (Q30-34)	0.45	·	0.12	·	0.06		0.09	·	0.00	·
Cleft lip/ palate (Q35-37)	0.00	·	0.27	·	0.18		0.17	·	0.13	·
Digestive system (Q38-45)	1.36	·	0.12	·	0.06		0.13	·	0.13	·
Genital organs (Q50-56)	0.51	·	0.01	·	0.02		0.02	·	0.00	·
Urinary system (Q60-64)	0.00	·	0.52	·	0.49		0.31	·	1.17	·
Musculoskeletal system (Q65-79)	0.90	·	0.64	·	0.49		0.50	·	0.26	·
Other and unspecified (Q80-89)	24.87	**8.35 (2.52-27.67)**	3.40	·	2.66		4.13	·	7.92	·
Chromosomal abnormalities (Q90-99)	4.07	·	1.87	·	3.39		10.11	·	20.64	**7.01 (2.09-23.52)**
Chromosomal abnormalities (Q90-99)*	4.07	·	1.87	·	3.39	·	10.11	**5 (1.10-22.84)**	20.64	**10.52 (2.47-44.88)**
Total	71.89	**6.59 (3.49-12.43)**	11.07	·	10.68		19.95	·	37.78	**3.46 (1.77-6.78)**

ICD, International classification of diseases, 10th revision; FMR, fetal mortality rate; OR, odd ratio; CI, confidence interval. FMRs by birth defects in group III were used as a reference for comparison with FMRs of other groups. *Comparison was performed between group II (reference) and the other groups. Statistically significant values were presented.

Figure 1. Infant mortality caused by birth defects, according to maternal age group.

Maternal age groups: ‘10-19 yr’ (I), ‘20-29 yr’ (II), ‘30-34 yr’ (III), ‘35-39 yr’ (IV), and ‘40-55 yr’ (V).

Figure 2. Fetal mortality caused by birth defects, according to maternal age group.

Maternal age groups: ‘10-19 yr’ (I), ‘20-29 yr’ (II), ‘30-34 yr’ (III), ‘35-39 yr’ (IV), and ‘40-55 yr’ (V).

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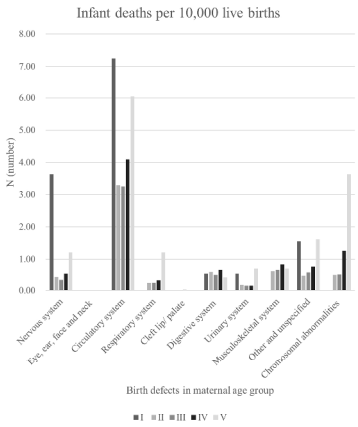

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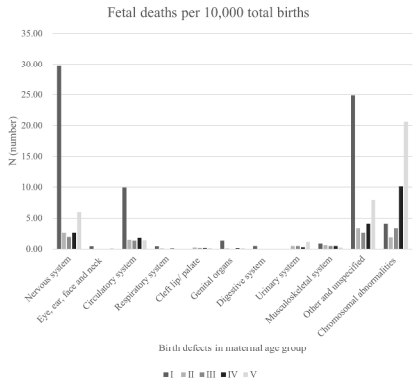
338x190mm (300 x 300 DPI)

Figure 2. Fetal mortality caused by birth defects, according to maternal age group.
Maternal age groups: '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).



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338x190mm (300 x 300 DPI)

Supplementary material.
Korean prevalence of fetal deaths and infant deaths caused by birth defect subtypes in 2009-2015

Birth defects (ICD-10)	N. of infant deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 livebirths	N. of fetal deaths caused by birth defect	Proportion (%) in birth defects	Prevalence per 10000 total births
Nervous system (Q00-07)						
Anencephaly (Q00.0-00.2)	37	1.70	0.12	213	4.90	0.66
Encephalocele (Q01.0-01.9)	3	0.14	0.01	32	0.74	0.10
Congenital Hydrocephalus (Q03.0-03.9)	34	1.56	0.11	157	3.62	0.49
Holoprosencephaly (Q04.0-04.2)	14	0.64	0.04	46	1.06	0.14
Other brain anomaly (Q43-49)	36	1.65	0.11	131	3.02	0.41
Spina bifida (Q05.0-05.9)	8	0.37	0.03	28	0.64	0.09
Other spinal anomaly (Q68-69)	0	0.00	0.00	3	0.07	0.01
Arnold-Chiari malformation (Q70)	1	0.05	0.00	18	0.41	0.06
Other nervous system anomaly (Q78-79)	3	0.14	0.01	206	4.74	0.64
Eye, ear, face and neck (Q10-18)	1	0.05	0.00	7	0.16	0.02
Circulatory system (Q20-28)						
Truncus arteriosus (Q20.0)	9	0.41	0.03	1	0.02	0.00
Double outlet right ventricle	66	3.03	0.21	7	0.16	0.02
Transposition of great arteries (Q20.1-20.3)	72	3.31	0.23	0	0.00	0.00
Double inlet ventricle (Q20.4)	58	2.67	0.18	1	0.02	0.00
Discordant atrioventricular connection (Q20.5)	2	0.09	0.01	1	0.02	0.00
Isomerism of atrial appendages (Q20.6)	3	0.14	0.01	1	0.02	0.00
Ventricular septal defect (Q21.0)	50	2.30	0.16	20	0.46	0.06
Atrial septal defect (Q21.1)	20	0.92	0.06	2	0.05	0.01
Atrioventricular septal defect (Q21.2)	72	3.31	0.23	4	0.09	0.01
Tetralogy of Fallot (Q21.3)	88	4.04	0.28	21	0.48	0.07
Other malformations of cardiac septa (Q21.4, 21.8, 21.9)	6	0.28	0.02	10	0.23	0.03
Pulmonary valve atresia/stenosis (Q22.0-22.1)	52	2.39	0.16	1	0.02	0.00
Congenital tricuspid stenosis (Q22.4)	5	0.23	0.02	1	0.02	0.00
Ebstein's anomaly (Q22.5)	23	1.06	0.07	7	0.16	0.02
Hypoplastic right heart syndrome (Q22.6)	1	0.05	0.00	1	0.02	0.00
Other malformations of tricuspid valve (Q22.8, 22.9)	3	0.14	0.01	4	0.09	0.01
Aortic valve stenosis/insufficiency (Q23.0, 23.1)	9	0.41	0.03	3	0.07	0.01

Mitral valve stenosis/insufficiency (Q23.2, 23.3)	8	0.37	0.03	0	0.00	0.00
Hypoplastic left heart syndrome (Q23.4)	86	3.95	0.27	7	0.16	0.02
Dextrocardia (Q 24.0)	0	0.00	0.00	3	0.07	0.01
Cor triatriaum (Q 24.2)	2	0.09	0.01	0	0.00	0.00
Subaortic stenosis (Q 24.4)	2	0.09	0.01	0	0.00	0.00
Malformation of coronary vessels (Q24.5-24.6)	6	0.28	0.02	0	0.00	0.00
Other heart malformation (Q24.2, 24.4-24.6)	88	4.04	0.28	50	1.15	0.16
Unspecified heart malformation (Q24.9)	75	3.45	0.24	299	6.88	0.93
Patent ductus arteriosus (Q25.0)*	87	4.00	0.27	0	0.00	0.00
Coarctation/atresia/stenosis of aorta (Q25.1-25.3)	55	2.53	0.17	0	0.00	0.00
Other malformations of aorta (Q25.4)	18	0.83	0.06	4	0.09	0.01
Pulmonary artery atresia/stenosis (Q25.5, 25.6)	22	1.01	0.07	2	0.05	0.01
Total anomalous pulmonary venous connection (Q26.2)	83	3.81	0.26	0	0.00	0.00
Partial anomalous pulmonary venous connection (Q26.3)	3	0.14	0.01	1	0.02	0.00
Peripheral arteriovenous malformation (Q27.3, 27.9, 27.9)	1	0.05	0.00	4	0.09	0.01
Malformations of cerebral vessels (Q 28.2, 28.3)	6	0.28	0.02	4	0.09	0.01
Other malformations of circulatory system (Q20.8, 20.9, 22.3, 25.7-26.1, 26.4, 27.0, 26.8, 28,8, 28.9)	31	1.42	0.10	34	0.78	0.11
Respiratory system (Q30-34)						
Other malformations of larynx, bronchus, trachea (Q31.0-32.4)	34	1.56	0.11	3	0.07	0.01
Congenital cystic lung (Q33.0)	5	0.23	0.02	5	0.12	0.02
Other malformation of lung (Q33.1-33.9)	42	1.93	0.13	16	0.37	0.05
Other malformations of respiratory system (Q34)	6	0.28	0.02	4	0.09	0.01
Cleft lip/palate (Q35-37)	3	0.14	0.01	64	1.47	0.20
Digestive system (Q38-45)						
Other malformation of mouths (Q38.5)	0	0.00	0.00	1	0.02	0.00
Esophageal atresia/stenosis (Q39.0-39.2)	34	1.56	0.11	6	0.14	0.02
Malformation of upper elimentary tract (Q40.0-40.9)	3	0.14	0.01	3	0.07	0.01
Duodenal atresia/stenosis (Q41.0)	3	0.14	0.01	7	0.16	0.02
Small intestine atresia/stenosis (Q41.1-41.9)	22	1.01	0.07	1	0.02	0.00
Anorectal atresia/stenosis (Q42.0-42.3)	2	0.09	0.01	2	0.05	0.01
Congenital megacolon (Q43.1)	44	2.02	0.14	0	0.00	0.00
Malrotation of colon (Q43.3)	9	0.41	0.03	0	0.00	0.00
Persistent cloaca (Q43.7)	1	0.05	0.00	2	0.05	0.01

Other intestinal and bile duct malformation (Q43.8-44.3)	42	1.93	0.13	6	0.14	0.02
Liver malformation (Q44.7)	4	0.18	0.01	0	0.00	0.00
Other malformation of digestive system (Q 42.8, 43.0, 45.8, 45.9)	5	0.23	0.02	6	0.14	0.02
Genital organs (Q50-56)	0	0.00	0.00	5	0.12	0.02
Urinary system (Q60-64)						
Renal agenesis (Q60.0-60.6)	22	1.01	0.07	44	1.01	0.14
Autosomal recessive polycystic kidney (Q61.1)	10	0.46	0.03	6	0.14	0.02
Unspecified polycystic kidney (Q61.3)	6	0.28	0.02	23	0.53	0.07
Renal dysplasia (Q61.4)	6	0.28	0.02	30	0.69	0.09
Cystic kidney (Q61.0, Q61.5-61.9)	1	0.05	0.00	3	0.07	0.01
Congenital hydronephrosis (Q62.0-62.8)	2	0.09	0.01	14	0.32	0.04
Other renal anomaly (Q63.0, 63.2, 63.8, 63.9)	3	0.14	0.01	30	0.69	0.09
Posterior urethral valve (Q64.2)	3	0.14	0.01	3	0.07	0.01
Congenital absence of bladder and urethra (Q64.5-64.9)	1	0.05	0.00	6	0.14	0.02
Musculoskeletal system (Q65-79)						
Club foot-talipes equinovarus (66.0)	0	0.00	0.00	1	0.02	0.00
Other congenital feet deformities (Q66.1-66.9)	0	0.00	0.00	4	0.09	0.01
Congenital deformities of skull, face, and jaw (Q67.0-67.4)	0	0.00	0.00	2	0.05	0.01
Pectus carinatum (Q67.6)	2	0.09	0.01	0	0.00	0.00
Other congenital musculoskeletal deformities (Q68.0-Q70.9)	0	0.00	0.00	12	0.28	0.04
Total limb reduction defects (Q71.0-71.9, Q72.0-72.9, Q73.0-73.8)	0	0.00	0.00	8	0.18	0.02
Other malformation of limbs and pelvic girdle (Q74.0-Q74.2, 74.8)	3	0.14	0.01	19	0.44	0.06
Arthrogryposis multiplex congenita (Q74.3)	4	0.18	0.01	1	0.02	0.00
Craniosynostosis (Q75.0)	6	0.28	0.02	0	0.00	0.00
Malformations of skul and face bones (Q75.1-75.9)	6	0.28	0.02	7	0.16	0.02
Klippel-Feil syndrome (Q76.1)	2	0.09	0.01	0	0.00	0.00
Malformations of spine and bony thorax (Q76.2-76.9)	2	0.09	0.01	7	0.16	0.02
Achondrogenesis/Hypochondrogenesis (Q77.0)	2	0.09	0.01	1	0.02	0.00
Thanatophoric dysplasia (Q77.1)	7	0.32	0.02	20	0.46	0.06
Asphyxiating thoracic dysplasia (Q77.2)	1	0.05	0.00	3	0.07	0.01
Achondroplasia/hypochondroplasia (Q77.4)	3	0.14	0.01	9	0.21	0.03
Osteogenesis imperfecta (Q78.0)	2	0.09	0.01	6	0.14	0.02

Other osteochondrodysplasia (Q77.8, 78.8, 78.9)	2	0.09	0.01	4	0.09	0.01
Diaphragmatic hernia (Q79.0)	138	6.34	0.43	22	0.51	0.07
Other malformations of diaphragm (Q79.1)	6	0.28	0.02	1	0.02	0.00
Omphalocele (Q79.2)	10	0.46	0.03	15	0.35	0.05
Gastroschisis (Q79.3)	8	0.37	0.03	12	0.28	0.04
Prune belly syndrome (Q79.4)	0	0.00	0.00	3	0.07	0.01
Other musculoskeletal anomaly (Q79.8, 79.9)	4	0.18	0.01	19	0.44	0.06
Other and unspecified (Q80-89)	186	8.55	0.58	1105	25.44	3.43
Chromosomal abnormalities (Q90-99)	220	10.11	0.69	1438	33.11	4.46

*Patent ductus arteriosus cases included 81 cases whose birthweight was less than 2,500 g.

N, number.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4,5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not applicable

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7,8,9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(*b*) Report category boundaries when continuous variables were categorized	7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.