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Infant and fetal mortality caused by birth defects in Korea

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Manuscripts

1 Infant and fetal mortality caused by birth defects in Korea

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

16
17 **Running title: Infant and fetal mortality caused by birth defects in Korea**

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

20 Key words: birth defect, infant, fetal, mortality, maternal age

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2
3 21 Abstract
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6 22 Objective: To analyze the prevalence of fetal and infant deaths due to birth defects in Korea and
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9 23 those trends according to maternal age.

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11 24 Design: Retrospective national cohort study

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15 25 Setting: Database in Korean vital Statistics, between 2009 and 2015.

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17
18 26 Participants: 2,176 infant deaths and 4,343 fetal deaths caused by birth defects, among 3,181,145
19
20 27 total live births and 43,385 fetal deaths during study periods

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22
23 28 Methods: Infant and fetal mortality rates (IMRs and FMRs) by birth defects, from deaths caused
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25
26 29 by birth defects, were analyzed. Those were compared, according to maternal age groups; '10-19
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28 30 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).

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30
31 31 Main Outcome Measures: IMRs and FMRs by birth defects and comparison according to
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33 32 maternal age group.

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36 33 Results: IMRs and FMRs by birth defects were 6.84 per 10,000 live births, and 13.47 per 10,000
37
38 34 total births. The most common causes of infant deaths and fetal deaths by birth defect were
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41 35 anomaly of circulatory system (51.1%, IMR 3.5) and chromosomal abnormality (33.1%, FMR
42
43 36 4.46), respectively. Among groups by maternal age, FMRs by birth defects were significantly
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46 37 higher in group I and V, compared to it in group III, (Odd ratio (OR) 6.59, 95% CI 3.49-12.43
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48 38 and 3.46, 95% CI 1.77-6.78, respectively). IMR and FMR by nervous system anomaly were
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51 39 significantly higher in group I, with 3.63 (OR 2.0, 95% CI 1.97-2.03) and 29.84 (OR15.04, 95%
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53 40 CI 3.59-62.96), compared to 0.32 and 1.97 in group III.
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3 41 Conclusion: FMRs by birth defects were the highest in extreme maternal age groups. Severe
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5 42 anomalies except chromosomal abnormality were the most prevalent in teenage pregnancies.
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10 11 12 44 Strengths and limitations of this study

- 14 45 • This study is the first one that reports infant and fetal mortalities caused by birth defects
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16 in Korea, from the national vital statistics.
- 17 46
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19 47 • This study compared the infant and fetal mortalities caused by birth defects, according to
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21 maternal age group, which showed higher prevalence of them in teenage pregnancies.
22 48
- 23
24 49 • The limitation of this study is that it does not show present prevalence of birth defects in
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26 live births.
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- 28
29 51 • This study supports a policy about mandatory folic acid fortification in Korea.
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32 33 34 53 **Introduction**

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36
37 54 Birth defects (structural abnormalities, sensory changes, chromosomal abnormalities, metabolic
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39 abnormalities, and neurodevelopmental defects) are presented in approximately 2-3% of all
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42 56 births [1-3]. Severe birth defects account for 20-25% of perinatal mortality and they are leading
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44 causes of infant mortality, abortion, and stillbirth [2-5]. During the last decade, screening tests
45 57
46 and ultrasonography during pregnancy have been developed to detect birth defects. However,
47 58
48 etiologies of 60-70% of birth defects remain unknown.
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52 60 In developed countries, birth defects surveillance systems have been developed to collect data on
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3 61 major structural birth defects and chromosomal abnormalities [6-8]. European registry reported
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5 62 that total and live birth prevalence of trisomies 21, 18 and 13 were increased between 1990 and
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8 63 2009, and those were mainly associated with increasing maternal age [9].
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11 64 While the number of live births in Korea has been decreased, maternal age has been increased
12
13 65 [10, 11]. The prevalence of birth defects in Korean live births has been reported before, using the
14
15 66 data based on the National Health Insurance Corporation on medical institutes across the country
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17 67 [12, 13]. However, it is important to include stillbirths and abortions in birth defects statistics
18
19 68 with total live births because birth defects occur during intrauterine life. Although it is hard to
20
21 69 include spontaneous abortion in the early stage of pregnancy, the investigation of fetal death
22
23 70 related with birth defect can be useful for estimating the prevalence of birth defects. In addition,
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25 71 investigation of infant death related to birth defect can be valuable information for counseling
26
27 72 parents, antenatally and postnatally.
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33 73 The aim of this study was to analyze the prevalence of fetal and infant deaths associated with
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35 74 birth defects, which are fetal/infant mortality rates (FMR/IMR) by birth defect, and evaluate
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37 75 changes of those prevalence rates, according to maternal age.
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41 **Materials and Methods**

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44 77 This study was conducted by utilizing deidentified data about fetal deaths, infant deaths, and live
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46 78 births between 2009 and 2015 from 'Korean Vital Statistics' of the Korean Statistical
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48 79 Information Service [10]. Korean Vital Statistics is a nationwide database developed to
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50 80 understand birth, death, marriage, and divorce in Korea. Data from Korean Vital Statistics are
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52 81 released monthly and annually via a press release, on website (<http://kosis.kr>), and in online
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54 82 publications, such as 'Annual Report on Vital Statistics.' From fetal and infant deaths data, fetal
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3 83 and infant death recorded as ‘a death caused by birth defect’ were included in fetal and infant
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5 84 deaths associated with birth defect. Fetal death was defined as intrauterine fetal death occurring
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8 85 after 16 weeks of gestational age and before the start of delivery or those occurring during labor.
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10 86 Infant death was defined as a death occurring within the first year of life.
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13 87 Birth defects were categorized by birth defect group (the system affected) and subtype
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15 (individual disease) according to the 10th Revision of the International Classification of Diseases
16 88 (ICD-10) and were investigated by including major groups of birth defects managed by
17 89 EUROCAT, ICBDSR, and the National Birth Defects Prevention Network (NBDPN). Deaths
18 90 caused by disease code ‘Q’ representing congenital disease were defined as fetal and infant
19 91 deaths related TO birth defect. According to the above standards, 2,176 infant deaths and 4,343
20 92 fetal deaths were caused by birth defect. This study calculated IMR by birth defects by dividing
21 93 the number of infant deaths related to birth defects by the total number of live births. It was
22 94 presented as the number per 10,000 live births as a standard. FMR by birth defects was
23 95 calculated by dividing the number of fetal deaths related with birth defect by the total number of
24 96 live births and fetal deaths, which presented as the number per 10,000 total births. Maternal age
25 97 groups were divided to the following five groups: ‘10-19 yr’ (I), ‘20-29 yr’ (II), ‘30-34 yr’ (III),
26 98 ‘35-39 yr’ (IV), and ‘40-55 yr’ (V). IMRs and FMRs by birth defects in group III were used as
27 99 control for comparison with IMRs/FMRs of other groups. For chromosomal abnormalites,
28 100 comparison was also performed between group II and the other groups.
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103 **Statistical analysis**

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3 104 Statistical calculations were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA),
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5 105 including means, proportions, odd ratio (OR), and 95% confidence intervals (CIs). Chi-square
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8 106 tests were performed to compare proportions of independent variables and t-tests were performed
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11 107 to compare means. Statistical significance was considered at $P < 0.05$ or if the 95% CI of OR did
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13 108 not include 1.

14 15 16 109 **Ethics statement**

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19 110 The study protocol was approved by the institutional review boards of Catholic University of
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21 111 Korea. Informed consent was waived by the board.
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36 116 **Results**

37 38 39 117 **Baseline characteristics**

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42 118 Total numbers of live births and fetal deaths in Korea from 2009 to 2015 were 3,181,145 and
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44 119 43,385, respectively. Among 9,563 infant deaths during the 7 years, the number of infant deaths
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47 120 related to birth defect was 2,176, accounting for 22.8% of all infant deaths. The number of fetal
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50 121 deaths related to birth defects was 4,343, accounting for 10.0% of all fetal deaths. Baseline
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52 122 demographic characteristics are summarized in Table 1.
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124 **IMRs, by birth defect groups and subtypes**

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

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139 **FMRs by birth defect groups and subtypes**

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

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3 145 malformation, and Edward syndrome, with FMR of 1.36, 0.93 and 0.82 per 10,000 total births,
4
5 146 respectively (Table 3&4).
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8 9 147 **IMRs and FMRs by birth defect groups, according to the maternal age group**

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11 148 In the analysis according to maternal age group, 2,529 live births, 113 fetal deaths not related to
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13 149 birth defects, and 12 fetal deaths related to birth defects were excluded due to missing values of
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15 150 maternal age. In infant deaths related to birth defect, anomaly of the circulatory system was most
16
17 151 common in all age groups (Table 5, Figure 1). IMRs of chromosomal abnormality seemed to be
18
19 152 increased in groups IV and V compared to that in group III. However, statistically significant
20
21 153 difference was only observed between group V and group III (OR 2.00 95% CI 1.97-2.03). The
22
23 154 IMR of nervous system anomaly was significantly higher in the youngest maternal age group
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25 155 (group I, 10-19 yr) with 3.63 per 10,000 live births (OR 2.0, 95% CI 1.97-2.03), compared to
26
27 156 that in group III (0.32 per 10,000 live births). In fetal deaths related to birth defect, most FMRs
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29 157 by birth defects were highest in the youngest group, except for FMR by chromosomal
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31 158 abnormality which was significantly higher in group V compared to that in group III (OR 7.01,
32
33 159 95% CI, 2.09-23.52) (Table 6, Figure 2). Compared to FMR of group II, FMRs of chromosomal
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35 160 abnormality were significantly higher in group IV and V (OR 5.00, 95% CI, 1.10-22.84 and OR
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37 161 10.52, 95% CI 2.47-44.88, respectively). FMRs by total birth defects were significantly higher in
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39 162 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
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41 163 1.77-6.78, respectively). Individually, FMRs for anomalies of nervous system and cardiovascular
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43 164 system, and, other and unspecified anomalies were significantly higher in group I, compared to
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45 165 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%
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47 166 CI 2.52-27.67, respectively)
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168 **Discussion**

169 It is important to know severe birth defects which can lead fetal and infant deaths and its
170 prevalence. Previously, the prevalence of birth defects in Korea in live births in 2005 and 2006
171 was reported to be approximately 2.9% [12], similar to those (2-3%) of other studies [1-3].
172 However, the other study reported the prevalence of birth defects in Korea in 2009 and 2010 as
173 5.8% [13]. Although there might be methodological limitation and variations, the prevalence of
174 birth defects in live births seems increasing. In this study, 22.8% of infant deaths of Korea were
175 related to birth defects. IMR and FMR caused by birth defects between 2009 and 2015 were 6.84
176 per 10,000 live births and 13.47 per 10,000 total births, respectively.

177 The most common birth defect group related to infant deaths was anomaly of the circulatory
178 system. However, the most common birth defect subtype was CDH. Despite advances in prenatal
179 diagnosis and neonatal intensive care including extracorporeal membrane oxygenation and
180 inhaled nitric oxide use, mortality rates due to CDH remain high, ranging from 50% to 70% with
181 great variability between centers [14-16]. The second most common birth defect in infant deaths
182 related to birth defect was TOF. The 10-year survival rate of TOF has been reported to be
183 approximately 95 % [17, 18]. When we consider the prevalence of TOF in live births in Korea
184 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
185 in this study, we can speculate that nationwide infant survival rates of TOF in Korea will be
186 approximately 93.3%, which is similar to that in the other reports [17, 18].

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

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3 189 maternal age groups (IV and V) compared to those in group II or III. FMRs due to birth defects
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5 190 were significantly higher in groups I and V compared to those in group III (OR: 6.59, 95% CI:
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7 191 3.49-12.43 and OR: 3.46, 95% CI: 1.77-6.78, respectively). FMR was much higher in group I.
8
9 192 Especially, IMR and FMR due to anomalies of the nervous system were significantly higher in
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11 193 group I compared with those in group III, indicating higher prevalence of severe anomalies of
12
13 194 nervous system in teenage pregnancies. In North America, fortification of flour and grain
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15 195 products became mandatory in 1998. Following folic acid fortification, prevalence of spina
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17 196 bifida birth in Canada fell by over 50% and that of other neural tube defects (NTDs) fell by
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19 197 approximately one-third [19]. In addition, the registry of 'European surveillance of congenital
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21 198 anomalies' has concluded that mandatory folic acid fortification is needed because the
22
23 199 prevalence of NTDs has not decreased in Europe despite longstanding recommendations aiming
24
25 200 at promoting periconceptional folic acid supplementation [20]. Results of Cochrane databases
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27 201 systematic review also showed a protective effect of daily folic acid supplementation in
28
29 202 preventing NTDs compared to no intervention/placebo or vitamins and minerals without folic
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31 203 acid (risk ratio 0.31, 95% CI 0.17- 0.58); five studies; 6708 births; high quality evidence) [21].
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33 204 Teenage pregnancies are more likely unplanned and exposed to alcohol, drug, sexual abuse, and
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35 205 nutritional imbalance. When pregnancies are complicated by birth defects in young age, they
36
37 206 might lead to termination of pregnancy (TOP), more easily. This study demonstrated increasing
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39 207 trends of IMRs and FMRs due to birth defects in the youngest and oldest maternal age groups.
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41 208 However, high IMRs and FMRs due to birth defects in the youngest age group were more
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43 209 pronounced except for chromosomal abnormality. Therefore, mandatory folic acid fortification
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45 210 in Korea might help reduce nervous system anomalies because the youngest age group is less
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3 211 likely to take periconceptional folic acid supplementation and the overall prevalence of spina
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6 212 bifida in Korea shows increasing tendency [13].
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9 213 In Europe, increasing trend of trisomy 13, 18, and 21 between 1990 and 2009 was reported [9].
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11 214 Because most TOPs with birth defects are illegal in Korea, it is almost impossible to estimate the
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13 215 proportions of TOP due to birth defects among fetal deaths. An international study has reported
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16 216 that the total mean prevalence of Down syndrome (still births, live births, and TOP) is increased
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18 217 from 13.1 to 18.2/10,000 births between 1993 and 2004 with increasing maternal age [22].
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21 218 However, the total mean prevalence of Down syndrome births remains stable at 8.3/10,000 births,
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23 219 balanced by a great increase of TOP [22]. Maternal age at conception has increased in Korea,
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25 220 although there are race/ethnic specific variations in birth defects [23]. IMR and FMR by Down
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27 221 syndrome was 0.27 per 10,000 live births and 1.78 per 10,000 total births, respectively. When we
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29
30 222 assume the prevalence of Down syndrome in as 3.7-4.7 per 10,000 live births from the previous
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32 223 studies in Korea [12, 13], infant survival rate of Down syndrome can be estimated approximately
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34 224 93.6%. Based on the increased prevalence of Down syndrome in the international study,
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37 225 according to increasing maternal age [22], we can expect that TOP due to Down syndrome may
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40 226 be also considerable in Korea.
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42 227 The limitation of this study is that it does not show present prevalence of birth defects in live
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44 228 births. Therefore, it is necessary to establish a comprehensive surveillance system with periodic
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46 229 production of data and monitoring to have effective prevention and management of birth defects.
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49 230 The second limitation of this study is that death cause of death registry is mostly made by
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51 231 clinician without autopsy. Because one or two disease codes are registered as the main code in
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53 232 death registry, multiple anomalies might have been included in one category. Lastly, this study
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56 233 did not include data on maternal nationality, paternal age, educational background, antenatal care,

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3 234 or parents' occupation due to high rates of missing values. However, this study is the first one
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5 235 that reports IMRs and FMRs caused by birth defects in Korea and different patterns according to
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8 236 maternal age group. Severe birth defects with high FMR were found to be more common in
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10 237 extreme maternal age groups (the youngest and the oldest). Except chromosomal abnormality,
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12 238 most severe anomalies, especially those of the nervous system and cardiovascular system, were
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15 239 more common in teenage pregnancies.
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17 240 As maternal age at conception is getting increased in Korea and screening tools are developing,
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19 241 prevalence and prenatal diagnosis of chromosomal anomalies are likely to be increased. Multi-
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21 242 disciplinary cooperation among government, politician, clinicians, and non-governmental
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23 243 organization is urgent not only for increasing fertility rate, but also for increasing healthy
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25 244 pregnancies with effective prevention and management of birth defects, especially for extreme
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27 245 maternal age groups and for supporting complicated pregnancies. A mandatory folic acid
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29 246 fortification needs to be discussed and considered in Korea.
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38 248 **Author contributions**

39
40 249 We confirm that all the authors have made substantive intellectual contributions to the paper;
41
42 250 they understand their role in taking responsibility and being accountable for what is published.
43
44 251 JCS conceptualized and reviewed the paper. HSK conceptualized the paper, gathered the results,
45
46 252 analyzed the data and wrote the article. YHC, JHW, SKC, and IYP analyzed the data and
47
48 253 reviewed the paper. YGP performed statistical analysis of the data.
49
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52 254

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3 256 This study was supported by Research Fund of Seoul St. Mary's Hospital, The Catholic
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6 257 University of Korea.

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9
10 259 **Conflict of Interest**

11
12 260 All authors have no conflict of interest related with this article.

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17 262 **Details of ethics approval**

18
19 263 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.

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

Chromosomal birth defects	Total N. of cases	Proportion	Prevalence	N. of infant deaths	Proportion	Prevalence	N. of fetal deaths	Proportion	Prevalence
	caused by birth defect	(%) in birth defects	per 10000 total births	caused by birth defect	(%) in birth defects	per 10000 live births	caused by birth defect	(%) in birth defects	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
Klinefelter'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 abnormalities	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

Maternal age group	IMR								
	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)
Birth defects (ICD-10)									
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.

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

Maternal age group	FMR									
	I (10-19 y)	OR (95% CI)	II (20-29 y)	OR (95% CI)	III (30-34 y)	OR (95% CI)	IV (35-39 y)	OR (95% CI)	V (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.

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

	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
Birth defects (ICD-10)						
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

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4	Hypoplastic left heart syndrome (Q23.4)	86	3.95	0.27	7	0.16	0.02
5	Dextrocardia (Q 24.0)	0	0.00	0.00	3	0.07	0.01
6	Cor triatrium (Q 24.2)	2	0.09	0.01	0	0.00	0.00
7	Subaortic stenosis (Q 24.4)	2	0.09	0.01	0	0.00	0.00
8	Malformation of coronary vessels (Q24.5-24.6)	6	0.28	0.02	0	0.00	0.00
9							
10	Other heart malformation (Q24.2, 24.4-24.6)	88	4.04	0.28	50	1.15	0.16
11	Unspecified heart malformation (Q24.9)	75	3.45	0.24	299	6.88	0.93
12	Patent ductus arteriosus (Q25.0)*	87	4.00	0.27	0	0.00	0.00
13	Coarctation/atresia/stenosis of aorta (Q25.1-25.3)	55	2.53	0.17	0	0.00	0.00
14	Other malformations of aorta (Q25.4)	18	0.83	0.06	4	0.09	0.01
15	Pulmonary artery atresia/stenosis (Q25.5, 25.6)	22	1.01	0.07	2	0.05	0.01
16	Total anomalous pulmonary venous connection (Q26.2)	83	3.81	0.26	0	0.00	0.00
17	Partial anomalous pulmonary venous connection (Q26.3)	3	0.14	0.01	1	0.02	0.00
18	Peripheral arteriovenous malformation (Q27.3, 27.9, 27.9)	1	0.05	0.00	4	0.09	0.01
19	Malformations of cerebral vessels (Q 28.2, 28.3)	6	0.28	0.02	4	0.09	0.01
20	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
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22	Respiratory system (Q30-34)						
23	Other malformations of larynx, bronchus, trachea (Q31.0-32.4)	34	1.56	0.11	3	0.07	0.01
24	Congenital cystic lung (Q33.0)	5	0.23	0.02	5	0.12	0.02
25	Other malformation of lung (Q33.1-33.9)	42	1.93	0.13	16	0.37	0.05
26	Other malformations of respiratory system (Q34)	6	0.28	0.02	4	0.09	0.01
27	Cleft lip/palate (Q35-37)	3	0.14	0.01	64	1.47	0.20
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29	Digestive system (Q38-45)						
30	Other malformation of mouths (Q38.5)	0	0.00	0.00	1	0.02	0.00
31	Esophageal atresia/stenosis (Q39.0-39.2)	34	1.56	0.11	6	0.14	0.02
32	Malformation of upper elementary tract (Q40.0-40.9)	3	0.14	0.01	3	0.07	0.01
33	Duodenal atresia/stenosis (Q41.0)	3	0.14	0.01	7	0.16	0.02
34	Small intestine atresia/stenosis (Q41.1-41.9)	22	1.01	0.07	1	0.02	0.00
35	Anorectal atresia/stenosis (Q42.0-42.3)	2	0.09	0.01	2	0.05	0.01
36	Congenital megacolon (Q43.1)	44	2.02	0.14	0	0.00	0.00
37	Malrotation of colon (Q43.3)	9	0.41	0.03	0	0.00	0.00
38	Persistent cloaca (Q43.7)	1	0.05	0.00	2	0.05	0.01
39	Other intestinal and bile duct malformation (Q43.8-44.3)	42	1.93	0.13	6	0.14	0.02
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4	Liver malformation (Q44.7)	4	0.18	0.01	0	0.00 0.00
5	Other malformation of digestive system (Q					
6	42.8, 43.0, 45.8, 45.9)	5	0.23	0.02	6	0.14 0.02
7	Genital organs (Q50-56)	0	0.00	0.00	5	0.12 0.02
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9	Urinary system (Q60-64)					
10	Renal agenesis (Q60.0-60.6)	22	1.01	0.07	44	1.01 0.14
11	Autosomal recessive polycystic kidney					
12	(Q61.1)	10	0.46	0.03	6	0.14 0.02
13	Unspecified polycystic kidney (Q61.3)	6	0.28	0.02	23	0.53 0.07
14	Renal dysplasia (Q61.4)	6	0.28	0.02	30	0.69 0.09
15	Cystic kidney (Q61.0, Q61.5-61.9)	1	0.05	0.00	3	0.07 0.01
16	Congenital hydronephrosis (Q62.0-62.8)	2	0.09	0.01	14	0.32 0.04
17	Other renal anomaly (Q63.0, 63.2, 63.8,					
18	63.9)	3	0.14	0.01	30	0.69 0.09
19	Posterior urethral valve (Q64.2)	3	0.14	0.01	3	0.07 0.01
20	Congenital absence of bladder and urethra					
21	(Q64.5-64.9)	1	0.05	0.00	6	0.14 0.02
22						
23	Musculoskeletal system (Q65-79)					
24						
25	Club foot-talipes equinovarus (66.0)	0	0.00	0.00	1	0.02 0.00
26	Other congenital feet deformities (Q66.1-					
27	66.9)	0	0.00	0.00	4	0.09 0.01
28	Congenital deformities of skull, face, and					
29	jaw (Q67.0-67.4)	0	0.00	0.00	2	0.05 0.01
30	Pectus carinatum (Q67.6)	2	0.09	0.01	0	0.00 0.00
31	Other congenital musculoskeletal					
32	deformities (Q68.0-Q70.9)	0	0.00	0.00	12	0.28 0.04
33	Total limb reduction defects (Q71.0-71.9,					
34	Q72.0-72.9, Q73.0-73.8)	0	0.00	0.00	8	0.18 0.02
35	Other malformation of limbs and pelvic					
36	girdle (Q74.0-Q74.2, 74.8)	3	0.14	0.01	19	0.44 0.06
37	Arthrogryposis multiplex congenita (Q74.3)	4	0.18	0.01	1	0.02 0.00
38	Craniosynostosis (Q75.0)	6	0.28	0.02	0	0.00 0.00
39	Malformations of skull and face bones					
40	(Q75.1-75.9)	6	0.28	0.02	7	0.16 0.02
41	Klippel-Feil syndrome (Q76.1)	2	0.09	0.01	0	0.00 0.00
42	Malformations of spine and bony thorax					
43	(Q76.2-76.9)	2	0.09	0.01	7	0.16 0.02
44	Achondrogenesis/Hypochondrogenesis					
45	(Q77.0)	2	0.09	0.01	1	0.02 0.00
46	Thanatophoric dysplasia (Q77.1)	7	0.32	0.02	20	0.46 0.06
47	Asphyxiating thoracic dysplasia (Q77.2)	1	0.05	0.00	3	0.07 0.01
48	Achondroplasia/hypochondroplasia (Q77.4)	3	0.14	0.01	9	0.21 0.03
49	Osteogenesis imperfecta (Q78.0)	2	0.09	0.01	6	0.14 0.02
50	Other osteochondrodysplasia (Q77.8, 78.8,					
51	78.9)	2	0.09	0.01	4	0.09 0.01
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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).

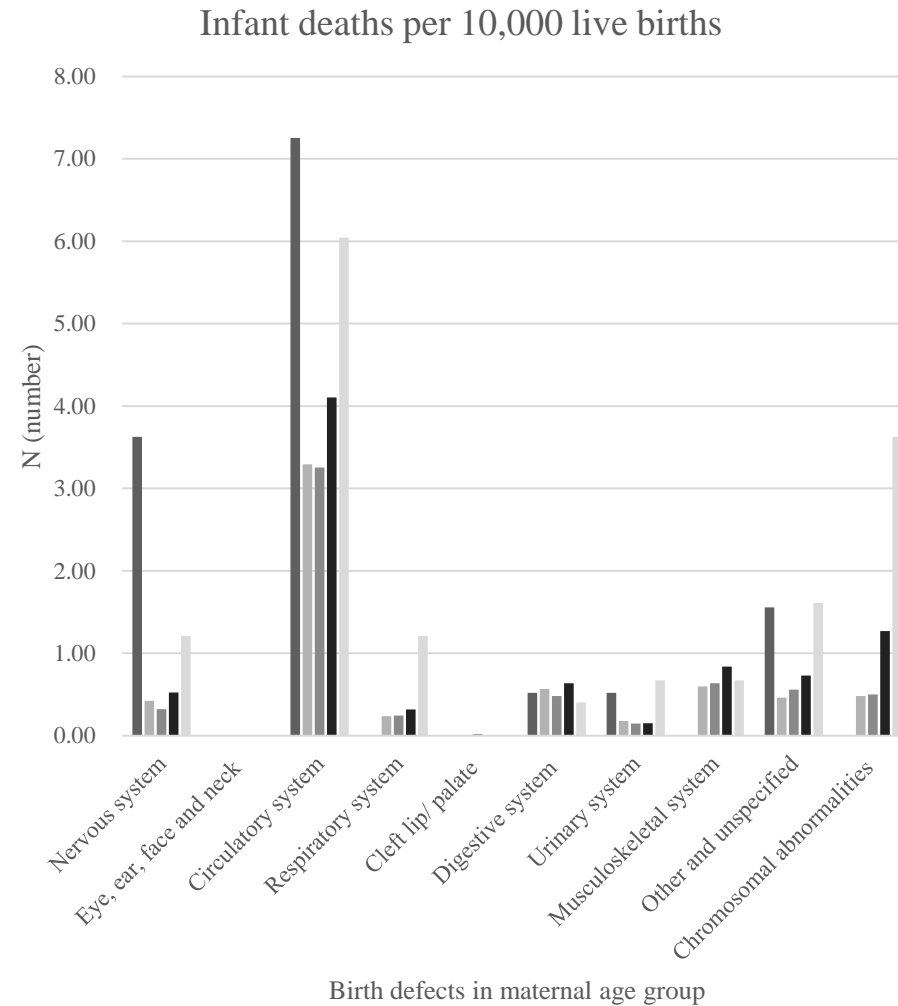
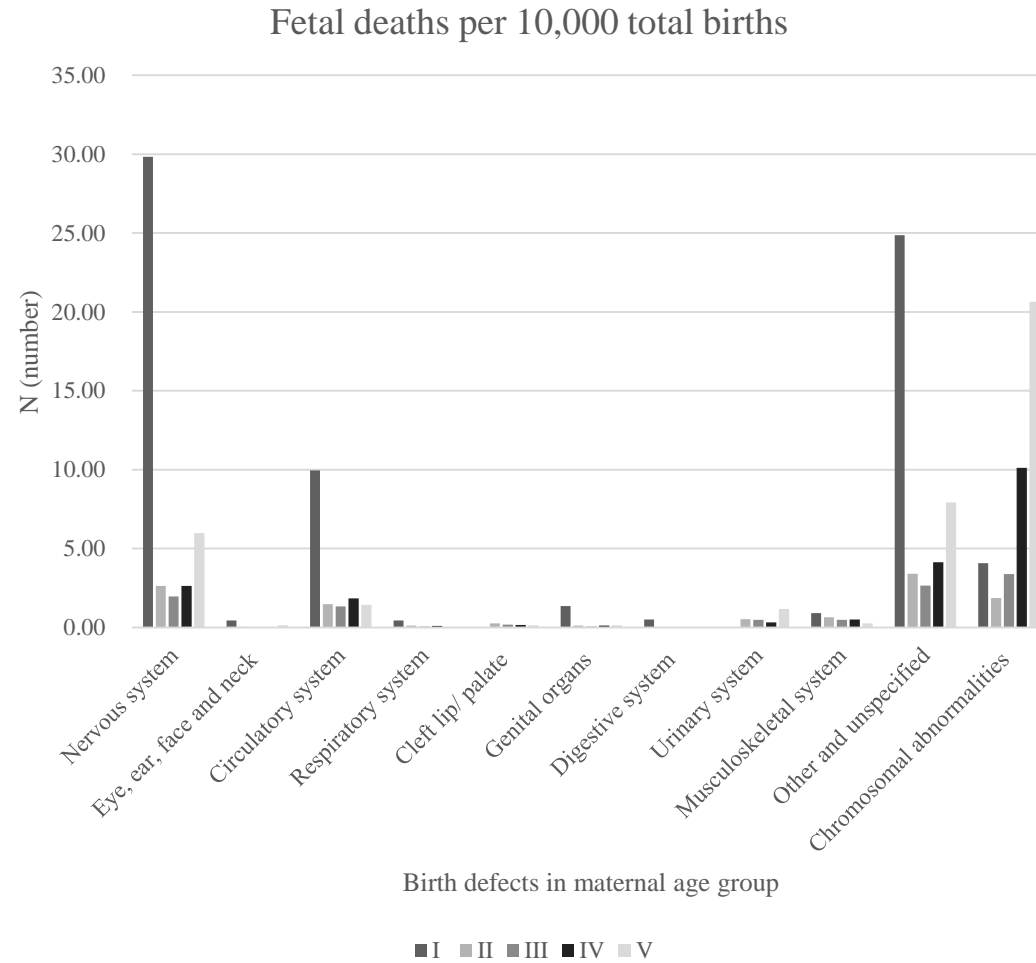


Figure 2. Fetal mortality caused by birth defects, according to maternal age group.

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) <i>Cohort study</i> — 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

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

1
2 70% with great variability between centers [14-16]. The second most common birth defect in
3 infant deaths related to birth defect was TOF. The 10-year survival rate of TOF has been
4 reported to be approximately 95 % [17, 18]. When we consider the prevalence of TOF in live
5 births in Korea with 4.1-4.2 per 10,000 live births [12, 13] and the IMR by TOF with 0.28 per
6 10,000 live births in this study, we can speculate that nationwide infant survival rates of TOF
7 in Korea will be approximately 93.3%, which is similar to that in the other reports [17, 18].
8

9 **Other information**

10
11 Funding 22 This study was supported by Research Fund of Seoul St. Mary's Hospital, The Catholic
12 University of Korea.
13

14 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and
15 unexposed groups in cohort and cross-sectional studies.
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18 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
19 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
20 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
21 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
22 available at www.strobe-statement.org.
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A national cohort study evaluating infant and fetal mortality caused by birth defects in Korea

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Keywords:	birth defect, infant, fetal, mortality, maternal age

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4 1 **A national cohort study evaluating infant and fetal mortality caused by birth defects in Korea**

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3 15 Key words; birth defect, infant death, fetal death, maternal age
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6 16 **Running title: Infant and fetal mortality caused by birth defects in Korea**
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9 17 Tweetable abstract: Severe anomalies except chromosomal abnormality were the most prevalent in teenage pregnancies.
10

11 18 Abstract
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15 19 Objective: To analyze the prevalence of fetal and infant deaths due to birth defects in Korea and those trends according to maternal
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17 20 age.
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20 21 Design: Retrospective national cohort study
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22 22 Setting: Database in Korean vital Statistics, between 2009 and 2015.
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24 23 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
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26 24 deaths during study periods
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31 25 Methods: Infant and fetal mortality rates (IMRs and FMRs) by birth defects, from deaths caused by birth defects, were analyzed.
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34 26 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'
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36 27 (V).
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39 28 Main Outcome Measures: IMRs and FMRs by birth defects and comparison according to maternal age group.
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3 29 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
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6 30 causes of infant deaths and fetal deaths by birth defect were anomaly of circulatory system (51.1%, IMR 3.5) and chromosomal
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8 31 abnormality (33.1%, FMR 4.46), respectively. Among groups by maternal age, FMRs by birth defects were significantly higher in
9
10 32 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
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12 33 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,
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14 34 95% CI 3.59-62.96), compared to 0.32 and 1.97 in group III.

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18 35 Conclusion: FMRs by birth defects were the highest in extreme maternal age groups. Severe anomalies except chromosomal
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20 36 abnormality were the most prevalent in teenage pregnancies.
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25 26 27 38 Strengths and limitations of this study

- 28
29 39 • This study is the first one that reports infant and fetal mortalities caused by birth defects in Korea, from the national vital
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31 40 statistics.
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33 41 • This study compared the infant and fetal mortalities caused by birth defects, according to maternal age group, which showed
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35 42 higher prevalence of them in teenage pregnancies.
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37 43 • The limitation of this study is that death cause of fetal/infant deaths were mostly diagnosed clinically without autopsy and
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39 44 there is no available data about spontaneous or induced abortion in fetal deaths.
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4 45 • The limitation of this study is that it does not show present prevalence of birth defects in live births.
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9 47 **Introduction**

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11 48 Birth defects (structural abnormalities, sensory changes, chromosomal abnormalities, metabolic abnormalities, and
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14 49 neurodevelopmental defects) are presented in approximately 2-3% of all births [1-3]. Severe birth defects account for 20-25% of
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17 50 perinatal mortality and they are leading causes of infant mortality, abortion, and stillbirth [2-5]. During the last decade, screening tests
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19 51 and ultrasonography during pregnancy have been developed to detect birth defects. However, etiologies of 60-70% of birth defects
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21 52 remain unknown.
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24 53 In developed countries, birth defects surveillance systems have been developed to collect data on
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27 54 major structural birth defects and chromosomal abnormalities [6-8]. European registry reported that total and live birth prevalence of
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30 55 trisomies 21, 18 and 13 were increased between 1990 and 2009, and those were mainly associated with increasing maternal age [9].
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33 56 While the number of live births in Korea has been decreased, maternal age has been increased [10, 11]. The prevalence of birth
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35 57 defects in Korean live births has been reported before, using the data based on the National Health Insurance Corporation on medical
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37 58 institutes across the country [12, 13]. However, it is important to include stillbirths and abortions in addition to live births to account
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39 59 for all pregnancies within birth defects. Although it is hard to include spontaneous abortion in the early stage of pregnancy, the
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3 60 investigation of fetal death related with birth defect can be useful for estimating the prevalence of birth defects. In addition,
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5 61 investigation of infant death related to birth defect can be valuable information for counseling parents, antenatally and postnatally.
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9 62 The aim of this study was to analyze the prevalence of fetal and infant deaths associated with birth defects, which are fetal/infant
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11 63 mortality rates (FMR/IMR) by birth defect, and evaluate changes of those prevalence rates, according to maternal age.
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14 64 **Materials and Methods**

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17 65 This national cohort study was conducted by utilizing deidentified data about fetal deaths, infant deaths, and live births between 2009
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19 66 and 2015 from 'Korean Vital Statistics' of the Korean Statistical Information Service [10]. Korean Vital Statistics is a nationwide
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21 67 database developed to understand birth, death, marriage, and divorce in Korea. Data from Korean Vital Statistics are released monthly
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23 68 and annually via a press release, on website (<http://kosis.kr>), and in online publications, such as 'Annual Report on Vital Statistics.'
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25 69 Since 2007, surveys and statistical analysis methods for infant and maternal death have been revised and complemented [14] to
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27 70 develop into a method for calculating more concrete, accurate numbers for fetal, infant, and maternal mortality rates in Korea. In
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29 71 summary, revision and supplementation of the statistics for fetal, infant and maternal death have been performed and validated by
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31 72 combination of official death registry data for vital statistics, survey data of public health center or medical institution, medical
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33 73 insurance claims database of the National Health Insurance Corporation on medical institutes across the country, and cremation
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35 74 reports data. Because national data about fetal death has been included since 2009, study cohort for this study was made by data
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37 75 between 2009 and 2015. However, data did not include information whether the cause of death was proven by autopsy. From fetal
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3 76 and infant deaths data, fetal and infant death recorded as ‘a death caused by birth defect’ were included in fetal and infant deaths
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5 77 associated with birth defect. Fetal deaths recorded as ‘termination of pregnancy (TOP)’ were excluded. Fetal death was defined as
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8 78 intrauterine fetal death occurring after 16 weeks of gestational age and before the start of delivery or those occurring during labor.
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10 79 Infant death was defined as a death occurring within the first year of life.
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13 80 Birth defects were categorized by birth defect group (the system affected) and subtype (individual disease) according to the 10th
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15 81 Revision of the International Classification of Diseases (ICD-10) and were investigated by including major groups of birth defects
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17 82 managed by EUROCAT, ICBDSR, and the National Birth Defects Prevention Network (NBDPN). Deaths caused by disease code ‘Q’
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19 83 representing congenital disease were defined as fetal and infant deaths related to birth defect. According to the above standards, 2,176
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21 84 infant deaths and 4,343 fetal deaths were caused by birth defect. This study calculated IMR by birth defects by dividing the number of
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23 85 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
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25 86 standard. FMR by birth defects was calculated by dividing the number of fetal deaths related with birth defect by the total number of
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27 87 live births and fetal deaths, which presented as the number per 10,000 total births. Maternal age groups were divided to the following
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29 88 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
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31 89 group III were used as control for comparison with IMRs/FMRs of other groups. For chromosomal abnormalities, comparison was
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33 90 also performed between group II and the other groups.
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3 92 **Statistical analysis**
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6 93 Statistical calculations were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA), including means, proportions, odd
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8 94 ratio (OR), and 95% confidence intervals (CIs). Chi-square tests were performed to compare proportions of independent variables and
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10 95 t-tests were performed to compare means. One decimal place was marked up in the presentation of maternal ages and gestational ages.
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12 96 Statistical significance was considered at $P < 0.05$ or if the 95% CI of OR did not include 1.
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16 97 **Ethics statement**
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19 98 The study protocol was approved by the institutional review board of Catholic University of Korea (KC17ZESI0409). Informed
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21 99 consent was waived by the board.
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37 104 **Results**
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40 105 **Baseline characteristics**
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3 106 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
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5 107 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
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7 108 deaths. 759 fetal deaths (1.75% of all fetal deaths) recorded as ‘TOP’ were excluded. The number of fetal deaths related to birth
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9 109 defects was 4,343, accounting for 10.0% of all fetal deaths. Baseline demographic characteristics are summarized in Table 1.
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111 **IMRs, by birth defect groups and subtypes**

112 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
113 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
114 common defects in infant deaths were chromosomal anomalies (0.69 per 10,000 live births, 10.1%) and musculoskeletal system
115 anomalies (0.65 per 10,000 live births, 9.6%). Among subtypes of birth defects, congenital diaphragmatic hernia (CDH) showed the
116 highest IMR at 0.43 per 10,000 live births (supplementary material). Among specified anomalies, lethal birth defects with the next
117 highest IMRs were Tetralogy of Fallot (TOF) and hypoplastic left heart syndrome (HLHS) (with IMRs of 0.28 and 0.27 per 10,000
118 live births, respectively). Among chromosomal anomalies, Down syndrome was the most common chromosomal abnormality with
119 IMR of 0.27 per 10,000 live births (Table 3).
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121 **FMRs by birth defect groups and subtypes**

122 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
123 were chromosomal anomalies, accounting for 33.1% of fetal deaths related to birth defect, and its FMR was 4.46 per 10,000 total births.
124 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
125 other chromosomal abnormality, unspecified congenital heart malformation, and Edward syndrome, with FMR of 1.36, 0.93 and 0.82
126 per 10,000 total births, respectively (Table 3 and supplementary material).

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

128 In the analysis according to maternal age group, 2,529 live births, 113 fetal deaths not related to birth defects, and 12 fetal deaths
129 related to birth defects were excluded due to missing values of maternal age. In infant deaths related to birth defect, anomaly of the
130 circulatory system was most common in all age groups (Table 4, Figure 1). IMRs of chromosomal abnormality seemed to be increased
131 in groups IV and V compared to that in group III. However, statistically significant difference was only observed between group V
132 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
133 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
134 10,000 live births). In fetal deaths related to birth defect, most FMRs by birth defects were highest in the youngest group, except for
135 FMR by chromosomal abnormality which was significantly higher in group V compared to that in group III (OR 7.01, 95% CI, 2.09-
136 23.52) (Table 5, Figure 2). Compared to FMR of group II, FMRs of chromosomal abnormality were significantly higher in group IV

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3 137 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
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6 138 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).
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8 139 Individually, FMRs for anomalies of nervous system and cardiovascular system, and, other and unspecified anomalies were
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10 140 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,
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12 141 95% CI 2.52-27.67, respectively)
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19 143 **Discussion**

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22 144 It is important to know severe birth defects which can lead fetal and infant deaths and its prevalence. Previously, the prevalence of
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24 145 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
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26 146 studies [1-3]. However, the other study reported the prevalence of birth defects in Korea in 2009 and 2010 as 5.8% [13]. Although
27
28 147 there might be methodological limitation and variations, the prenatal and postnatal detection rates of birth defects in live births seems
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30 148 increasing. In this study, 22.8% of infant deaths of Korea were related to birth defects. IMR and FMR caused by birth defects between
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32 149 2009 and 2015 were 6.84 per 10,000 live births and 13.47 per 10,000 total births, respectively.
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36 150 The most common birth defect group related to infant deaths was anomaly of the circulatory system. However, the most common birth
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38 151 defect subtype was CDH. Despite advances in prenatal diagnosis and neonatal intensive care including extracorporeal membrane
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40 152 oxygenation and inhaled nitric oxide use, mortality rates due to CDH remain high, ranging from 50% to 70% with great variability
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3 153 between centers [15-17]. The second most common birth defect in infant deaths related to birth defect was TOF. The 10-year survival
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5 154 rate of TOF has been reported to be approximately 95 % [18, 19]. When we consider the prevalence of TOF in live births in Korea
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8 155 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
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10 156 nationwide infant survival rates of TOF in Korea will be approximately 93.3%, which is similar to that in the other reports [18, 19].
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13 157 As expected, when IMRs and FMRs caused by birth defects were compared according to maternal age group, IMRs and FMRs due
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15 158 to chromosomal abnormality were higher in older maternal age groups (IV and V) compared to those in group II or III. FMRs due to
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17 159 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,
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19 160 95% CI: 1.77-6.78, respectively). FMR was much higher in group I. Especially, IMR and FMR due to anomalies of the nervous
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21 161 system were significantly higher in group I compared with those in group III, indicating higher prevalence of severe anomalies of
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23 162 nervous system in teenage pregnancies. In North America, fortification of flour and grain products became mandatory in 1998.
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25 163 Following folic acid fortification, prevalence of spina bifida birth in Canada fell by over 50% and that of other neural tube defects
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27 164 (NTDs) fell by approximately one-third [20]. In addition, the registry of 'European surveillance of congenital anomalies' has
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29 165 concluded that mandatory folic acid fortification is needed because the prevalence of NTDs has not decreased in Europe despite
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31 166 longstanding recommendations aiming at promoting periconceptional folic acid supplementation [21]. Results of Cochrane databases
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33 167 systematic review also showed a protective effect of daily folic acid supplementation in preventing NTDs compared to no
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35 168 intervention/placebo or vitamins and minerals without folic acid (risk ratio 0.31, 95% CI 0.17- 0.58); five studies; 6708 births; high
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3 169 quality evidence) [22]. Teenage pregnancies are more likely unplanned and exposed to alcohol, drug, sexual abuse, and nutritional
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6 170 imbalance. When pregnancies are complicated by birth defects in young age, they might lead to TOP, more easily. This study
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8 171 demonstrated increasing trends of IMRs and FMRs due to birth defects in the youngest and oldest maternal age groups. However, high
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10 172 IMRs and FMRs due to birth defects in the youngest age group were more pronounced except for chromosomal abnormality. It is
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12 173 known that adolescent pregnancy is associated with higher risks of adverse neonatal outcomes, such as low birth weight, preterm
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14 174 delivery [23]. In regard to birth defects, gastroschisis has been shown to be higher in young mothers [24, 25]. However, there has been
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16 175 no other associations between young maternal age and any other birth defect, to our knowledge. Although it is unclear whether high
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18 176 IMRs and FMRs related to birth defects in the youngest maternal age group in this study are associated maternal age, or other social,
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20 177 nutritional, and environmental factors, further investigation might be needed in the future. In addition, mandatory folic acid
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22 178 fortification in Korea might help reduce nervous system anomalies because the youngest age group is less likely to take
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24 179 periconceptional folic acid supplementation and the overall prevalence of spina bifida in Korea shows increasing tendency [13].
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30 180 In Europe, increasing trend of trisomy 13, 18, and 21 between 1990 and 2009 was reported [9]. In Korea, most of prenatal screening
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32 181 methods are available, such as the first trimester combined test, Quad screening, integrated, sequential test and cell-free DNA
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34 182 screening [26]. However, the legally acceptable pregnancy termination is very restrictive in Korea. The maternal and child health law
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36 183 only permits an abortion for one of the following reasons; if the pregnant woman or her spouse suffers from an eugenic or hereditary
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38 184 mental or physical disease specified by presidential decree, if the woman or her spouse suffers from a communicable disease specified
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3 185 by presidential decree, if the pregnancy results from rape or incest or if continuation of the pregnancy is likely to jeopardize the
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5 186 mother's health. Therefore, it is almost impossible to estimate the proportions of TOP due to birth defects among fetal deaths. An
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8 187 international study has reported that the total mean prevalence of Down syndrome (still births, live births, and TOP) is increased from
9
10 188 13.1 to 18.2/10,000 births between 1993 and 2004 with increasing maternal age [27]. However, the total mean prevalence of Down
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12 189 syndrome births remains stable at 8.3/10,000 births, balanced by a great increase of TOP [27]. Maternal age at conception has
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14 190 increased in Korea, although there are race/ethnic specific variations in birth defects [28]. IMR and FMR by Down syndrome was 0.27
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16 191 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
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18 192 per 10,000 live births from the previous studies in Korea [12, 13], infant survival rate of Down syndrome can be estimated
19
20 193 approximately 93.6%. Based on the increased prevalence of Down syndrome in the international study, according to increasing
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22 194 maternal age [27], we can expect that TOP due to Down syndrome may be also considerable in Korea.
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26 195 The first limitation of this study is that death cause of fetal/infant deaths might be mostly made by clinician without autopsy. Although
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28 196 most autopsies performed in the Republic of Korea are forensic autopsies, the autopsy rates for total mortality and unusual death in
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30 197 Korea were reported as 2.4% and 18.1%, respectively, in 2015, which were very low [29, 30]. It could be related with the
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32 198 overwhelming majority of fetal losses due to unspecified nervous, cardiovascular, and other system. Because one or two disease
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34 199 codes are registered as the main code in death registry, multiple anomalies might have been included in one category. The second
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36 200 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
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38 201 comprehensive surveillance system with periodic production of data and monitoring to have effective prevention and management of
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3 202 birth defects. Lastly, this study did not include data on maternal nationality, paternal age, educational background, antenatal care, or
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5 203 parents' occupation due to high rates of missing values. However, this study is the first one that reports IMRs and FMRs caused by
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7 204 birth defects in Korea and different patterns according to maternal age group. Severe birth defects with high FMR were found to be
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9 205 more common in extreme maternal age groups (the youngest and the oldest). Except chromosomal abnormality, most severe
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11 206 anomalies, especially those of the nervous system and cardiovascular system, were more common in teenage pregnancies.
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15 207 As maternal age at conception is getting increased in Korea and screening tools are developing, prevalence and prenatal diagnosis of
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17 208 chromosomal anomalies are likely to be increased. Multi-disciplinary cooperation among government, politician, clinicians, and non-
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19 209 governmental organization is urgent not only for increasing fertility rate, but also for increasing healthy pregnancies with effective
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21 210 prevention and management of birth defects, especially for extreme maternal age groups and for supporting complicated pregnancies.
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23 211 A mandatory folic acid fortification needs to be discussed and considered in Korea.
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30 213 **Author contributions**

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33 214 We confirm that all the authors have made substantive intellectual contributions to the paper; they understand their role in taking
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35 215 responsibility and being accountable for what is published. JCS conceptualized and reviewed the paper. HSK and DJK conceptualized
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37 216 the paper, gathered the results, analyzed the data and wrote the article. YHC, JHW, SKC, and IYP analyzed the data and reviewed the
38
39 217 paper. YGP performed statistical analysis of the data.
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10 221
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12 222 **Conflict of Interest**
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15 223 All authors have no conflict of interest related with this article.
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19 225 **Details of ethics approval**
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22 226 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	Proportion	Prevalence	N. of infant deaths	Proportion	Prevalence	N. of fetal deaths	Proportion	Prevalence
	caused by birth defect	(%) in birth defects	per 10000 total births	caused by birth defect	(%) in birth defects	per 10000 live births	caused by birth defect	(%) in birth defects	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
Klinefelter'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 abnormalities	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

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

Maternal age group	IMR									
	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.

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

Maternal age group	FMR									
	I (10-19 y)	OR (95% CI)	II (20-29 y)	OR (95% CI)	III (30-34 y)	OR (95% CI)	IV (35-39 y)	OR (95% CI)	V (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.

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

333 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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338 Figure 2. Fetal mortality caused by birth defects, according to maternal age group.

339 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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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).

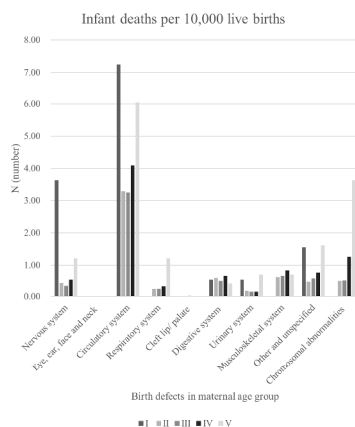


Figure 1. Infant mortality caused by birth defects, according to maternal age group.
 Maternal age groups: '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).

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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).

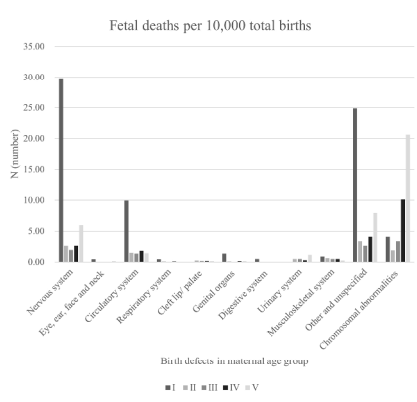


Figure 2. Fetal mortality caused by birth defects, according to maternal age group.
Maternal age groups: '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).

338x190mm (300 x 300 DPI)

Review only

Supplementary material.

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

	N. of infant deaths	Proportion	Prevalence	N. of fetal deaths	Proportion	Prevalence
Birth defects (ICD-10)	caused by	(%) in	per 10000	caused by	(%) in	per 10000
	birth defect	birth	livebirths	birth defect	birth	total births
	defects	defects		defects	defects	
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

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4	Mitral valve stenosis/insufficiency (Q23.2, 23.3)	8	0.37	0.03	0	0.00	0.00
5	Hypoplastic left heart syndrome (Q23.4)	86	3.95	0.27	7	0.16	0.02
6	Dextrocardia (Q 24.0)	0	0.00	0.00	3	0.07	0.01
7	Cor triatrium (Q 24.2)	2	0.09	0.01	0	0.00	0.00
8							
9	Subaortic stenosis (Q 24.4)	2	0.09	0.01	0	0.00	0.00
10							
11	Malformation of coronary vessels (Q24.5-24.6)	6	0.28	0.02	0	0.00	0.00
12							
13	Other heart malformation (Q24.2, 24.4-24.6)	88	4.04	0.28	50	1.15	0.16
14	Unspecified heart malformation (Q24.9)	75	3.45	0.24	299	6.88	0.93
15	Patent ductus arteriosus (Q25.0)*	87	4.00	0.27	0	0.00	0.00
16							
17	Coarctation/atresia/stenosis of aorta (Q25.1-25.3)	55	2.53	0.17	0	0.00	0.00
18							
19	Other malformations of aorta (Q25.4)	18	0.83	0.06	4	0.09	0.01
20							
21	Pulmonary artery atresia/stenosis (Q25.5, 25.6)	22	1.01	0.07	2	0.05	0.01
22							
23	Total anomalous pulmonary venous connection (Q26.2)	83	3.81	0.26	0	0.00	0.00
24	Partial anomalous pulmonary venous connection (Q26.3)	3	0.14	0.01	1	0.02	0.00
25	Peripheral arteriovenous malformation (Q27.3, 27.9, 27.9)	1	0.05	0.00	4	0.09	0.01
26							
27	Malformations of cerebral vessels (Q 28.2, 28.3)	6	0.28	0.02	4	0.09	0.01
28							
29	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
30							
31							
32	Respiratory system (Q30-34)						
33	Other malformations of larynx, bronchus, trachea (Q31.0-32.4)	34	1.56	0.11	3	0.07	0.01
34							
35	Congenital cystic lung (Q33.0)	5	0.23	0.02	5	0.12	0.02
36							
37	Other malformation of lung (Q33.1-33.9)	42	1.93	0.13	16	0.37	0.05
38	Other malformations of respiratory system (Q34)	6	0.28	0.02	4	0.09	0.01
39							
40	Cleft lip/palate (Q35-37)	3	0.14	0.01	64	1.47	0.20
41							
42	Digestive system (Q38-45)						
43	Other malformation of mouths (Q38.5)	0	0.00	0.00	1	0.02	0.00
44							
45	Esophageal atresia/stenosis (Q39.0-39.2)	34	1.56	0.11	6	0.14	0.02
46	Malformation of upper elementary tract (Q40.0-40.9)	3	0.14	0.01	3	0.07	0.01
47							
48	Duodenal atresia/stenosis (Q41.0)	3	0.14	0.01	7	0.16	0.02
49							
50	Small intestine atresia/stenosis (Q41.1-41.9)	22	1.01	0.07	1	0.02	0.00
51							
52	Anorectal atresia/stenosis (Q42.0-42.3)	2	0.09	0.01	2	0.05	0.01
53							
54	Congenital megacolon (Q43.1)	44	2.02	0.14	0	0.00	0.00
55	Malrotation of colon (Q43.3)	9	0.41	0.03	0	0.00	0.00
56							
57	Persistent cloaca (Q43.7)	1	0.05	0.00	2	0.05	0.01
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4	Other intestinal and bile duct malformation (Q43.8-44.3)	42	1.93	0.13	6	0.14 0.02
5	Liver malformation (Q44.7)	4	0.18	0.01	0	0.00 0.00
6						
7	Other malformation of digestive system (Q 42.8, 43.0, 45.8, 45.9)	5	0.23	0.02	6	0.14 0.02
8						
9	Genital organs (Q50-56)	0	0.00	0.00	5	0.12 0.02
10						
11	Urinary system (Q60-64)					
12	Renal agenesis (Q60.0-60.6)	22	1.01	0.07	44	1.01 0.14
13	Autosomal recessive polycystic kidney (Q61.1)	10	0.46	0.03	6	0.14 0.02
14	Unspecified polycystic kidney (Q61.3)	6	0.28	0.02	23	0.53 0.07
15	Renal dysplasia (Q61.4)	6	0.28	0.02	30	0.69 0.09
16	Cystic kidney (Q61.0, Q61.5-61.9)	1	0.05	0.00	3	0.07 0.01
17	Congenital hydronephrosis (Q62.0-62.8)	2	0.09	0.01	14	0.32 0.04
18	Other renal anomaly (Q63.0, 63.2, 63.8, 63.9)	3	0.14	0.01	30	0.69 0.09
19	Posterior urethral valve (Q64.2)	3	0.14	0.01	3	0.07 0.01
20	Congenital absence of bladder and urethra (Q64.5-64.9)	1	0.05	0.00	6	0.14 0.02
21						
22	Musculoskeletal system (Q65-79)					
23						
24	Club foot-talipes equinovarus (66.0)	0	0.00	0.00	1	0.02 0.00
25	Other congenital feet deformities (Q66.1-66.9)	0	0.00	0.00	4	0.09 0.01
26	Congenital deformities of skull, face, and jaw (Q67.0-67.4)	0	0.00	0.00	2	0.05 0.01
27	Pectus carinatum (Q67.6)	2	0.09	0.01	0	0.00 0.00
28	Other congenital musculoskeletal deformities (Q68.0-Q70.9)	0	0.00	0.00	12	0.28 0.04
29	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
30	Other malformation of limbs and pelvic girdle (Q74.0-Q74.2, 74.8)	3	0.14	0.01	19	0.44 0.06
31	Arthrogryposis multiplex congenita (Q74.3)	4	0.18	0.01	1	0.02 0.00
32	Craniosynostosis (Q75.0)	6	0.28	0.02	0	0.00 0.00
33	Malformations of skull and face bones (Q75.1-75.9)	6	0.28	0.02	7	0.16 0.02
34	Klippel-Feil syndrome (Q76.1)	2	0.09	0.01	0	0.00 0.00
35	Malformations of spine and bony thorax (Q76.2-76.9)	2	0.09	0.01	7	0.16 0.02
36	Achondrogenesis/Hypochondrogenesis (Q77.0)	2	0.09	0.01	1	0.02 0.00
37	Thanatophoric dysplasia (Q77.1)	7	0.32	0.02	20	0.46 0.06
38	Asphyxiating thoracic dysplasia (Q77.2)	1	0.05	0.00	3	0.07 0.01
39	Achondroplasia/hypochondroplasia (Q77.4)	3	0.14	0.01	9	0.21 0.03
40	Osteogenesis imperfecta (Q78.0)	2	0.09	0.01	6	0.14 0.02
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4	Other osteochondrodysplasia (Q77.8, 78.8, 78.9)	2	0.09	0.01	4	0.09	0.01
5	Diaphragmatic hernia (Q79.0)	138	6.34	0.43	22	0.51	0.07
6	Other malformations of diaphragm (Q79.1)	6	0.28	0.02	1	0.02	0.00
7	Omphalocele (Q79.2)	10	0.46	0.03	15	0.35	0.05
8	Gastroschisis (Q79.3)	8	0.37	0.03	12	0.28	0.04
9	Prune belly syndrome (Q79.4)	0	0.00	0.00	3	0.07	0.01
10	Other musculoskeletal anomaly (Q79.8, 79.9)	4	0.18	0.01	19	0.44	0.06
11	Other and unspecified (Q80-89)	186	8.55	0.58	1105	25.44	3.43
12	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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4,5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	Not applicable

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7,8,9
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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

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Keywords:	birth defect, infant, fetal, mortality, maternal age

SCHOLARONE™
Manuscripts

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4 1 **A national cohort study evaluating infant and fetal mortality caused by birth defects in Korea**

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7 2 Hyun Sun Ko,^{1#} Dong Joo Kim,^{2,3#} Yoohyun Chung,¹ Jeong Ha Wie,¹ Sae Kyung Choi,¹ In Yang Park,¹ Yong-gyu Park,⁴ Jong Chul

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2
3 15 Key words; birth defect, infant death, fetal death, maternal age
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6 16 **Running title: Infant and fetal mortality caused by birth defects in Korea**
7

8
9 17 Tweetable abstract: Severe anomalies except chromosomal abnormality were the most prevalent in teenage pregnancies.
10

11 18 Abstract
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15 19 Objective: To analyze the prevalence of fetal and infant deaths due to birth defects in Korea and those trends according to maternal
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17 20 age.
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20 21 Design: Retrospective national cohort study
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22 22 Setting: Database in Korean vital Statistics, between 2009 and 2015.
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24 23 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
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26 24 deaths during study periods
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31 25 Methods: Infant and fetal mortality rates (IMRs and FMRs) by birth defects, from deaths caused by birth defects, were analyzed.
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34 26 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'
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36 27 (V).
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39 28 Main Outcome Measures: IMRs and FMRs by birth defects and comparison according to maternal age group.
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3 29 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
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5 30 causes of infant deaths and fetal deaths by birth defect were anomaly of circulatory system (51.1%, IMR 3.5) and chromosomal
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7 31 abnormality (33.1%, FMR 4.46), respectively. Among groups by maternal age, FMRs by birth defects were significantly higher in
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9 32 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
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11 33 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,
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13 34 95% CI 3.59-62.96), compared to 0.32 and 1.97 in group III.
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18 35 Conclusion: FMRs by birth defects were the highest in extreme maternal age groups. Severe anomalies except chromosomal
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20 36 abnormality were the most prevalent in teenage pregnancies.
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27 38 Strengths and limitations of this study

- 29 39 • This study is the first one that reports infant and fetal mortalities caused by birth defects in Korea, from the national vital
30 40 statistics.
- 31 41 • This study compared the infant and fetal mortalities caused by birth defects, according to maternal age group, which showed
32 42 higher prevalence of them in teenage pregnancies.
- 33 43 • The limitation of this study is that causes of fetal/infant deaths were mostly diagnosed clinically without autopsy and there is
34 44 no available data about spontaneous or induced abortion in fetal deaths.

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3 45 • The limitation of this study is that it does not show present prevalence of birth defects in live births.
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9 47 **Introduction**

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11 48 Birth defects (structural abnormalities, sensory changes, chromosomal abnormalities, metabolic abnormalities, and
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14 49 neurodevelopmental defects) are presented in approximately 2-3% of all births [1-3]. Severe birth defects account for 20-25% of
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17 50 perinatal mortality and they are leading causes of infant mortality, abortion, and stillbirth [2-5]. During the last decade, screening tests
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19 51 and ultrasonography during pregnancy have been developed to detect birth defects. However, etiologies of 60-70% of birth defects
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21 52 remain unknown.
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24 53 In developed countries, birth defects surveillance systems have been developed to collect data on major structural birth defects and
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27 54 chromosomal abnormalities [6-8]. European registry reported that total and live birth prevalence of trisomies 21, 18 and 13 were
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29 55 increased between 1990 and 2009, and those were mainly associated with increasing maternal age [9].
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32 56 While the number of live births in Korea has been decreased, the number of maternal age has been increased [10, 11]. The prevalence
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34 57 of birth defects in Korean live births has been reported before, using the data based on the National Health Insurance Corporation and
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37 58 medical institutes across the country [12, 13]. However, it is important to include stillbirths in addition to live births to account for all
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39 59 pregnancies within birth defects. Although it is hard to include spontaneous abortion in the early stage of pregnancy, the investigation
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3 60 of fetal death related with birth defect can be useful for estimating the prevalence of birth defects. In addition, investigation of infant
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5 61 death related to birth defect can be valuable information for counseling parents, antenatally and postnatally.
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9 62 The aim of this study was to analyze the prevalence of fetal and infant deaths associated with birth defects, which are fetal/infant
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11 63 mortality rates (FMR/IMR) by birth defect, and evaluate changes of those prevalence rates, according to maternal age.
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14 64 **Materials and Methods**

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17 65 This national cohort study was conducted by utilizing deidentified data about fetal deaths, infant deaths, and live births between 2009
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19 66 and 2015 from 'Korean Vital Statistics' of the Korean Statistical Information Service [10]. Korean Vital Statistics is a nationwide
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21 67 database developed to understand birth, death, marriage, and divorce in Korea. Data from Korean Vital Statistics are released monthly
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23 68 and annually via a press release, on website (<http://kosis.kr>), and in online publications, such as 'Annual Report on Vital Statistics.'
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25 69 Since 2007, surveys and statistical analysis methods for infant and maternal death have been revised and complemented [14] to
26
27 70 develop into a method for calculating more concrete, accurate numbers for fetal, infant, and maternal mortality rates in Korea. In
28
29 71 summary, revision and supplementation of the statistics for fetal, infant and maternal death have been performed and validated by
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31 72 combination of official death registry data for vital statistics, survey data of public health center or medical institution, medical
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33 73 insurance claims database of the National Health Insurance Corporation on medical institutes across the country, and cremation
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35 74 reports data. Because national data about fetal death has been included since 2009, study cohort for this study was made by data
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37 75 between 2009 and 2015. However, data did not include information whether the cause of death was proven by autopsy. From fetal
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3 76 and infant deaths data, fetal and infant death recorded as ‘a death caused by birth defect’ were included in fetal and infant deaths
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5 77 associated with birth defect. Fetal death was defined as intrauterine fetal death occurring after 16 weeks of gestational age and before
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7 78 the start of delivery or those occurring during labor. Infant death was defined as a death occurring within the first year of life.
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11 79 Birth defects were categorized by birth defect group (the system affected) and subtype (individual disease) according to the 10th
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13 80 Revision of the International Classification of Diseases (ICD-10) and were investigated by including major groups of birth defects
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15 81 managed by EUROCAT, ICBDSR, and the National Birth Defects Prevention Network (NBDPN). Deaths caused by disease code ‘Q’
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17 82 representing congenital disease were defined as fetal and infant deaths related to birth defect. According to the above standards, 2,176
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19 83 infant deaths and 4,343 fetal deaths were caused by birth defect. This study calculated IMR by birth defects by dividing the number of
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21 84 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
22
23 85 standard. FMR by birth defects was calculated by dividing the number of fetal deaths related with birth defect by the total number of
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25 86 live births and fetal deaths, which presented as the number per 10,000 total births. Maternal age groups were divided to the following
26
27 87 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
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29 88 group III were used as control for comparison with IMRs/FMRs of other groups. For chromosomal abnormalities, comparison was
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31 89 also performed between group II and the other groups.
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41 91 **Statistical analysis**

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3 92 Statistical calculations were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA), including means, proportions, odd
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5 93 ratio (OR), and 95% confidence intervals (CIs). Chi-square tests were performed to compare proportions of independent variables and
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8 94 t-tests were performed to compare means. One decimal place was marked up in the presentation of maternal ages and gestational ages.
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10 95 Statistical significance was considered at $P < 0.05$ or if the 95% CI of OR did not include 1.
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13 96 **Ethics statement**

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16 97 The study protocol was approved by the institutional review board of Catholic University of Korea (KC17ZESI0409). Informed
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18 98 consent was waived by the board.
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106 **Results**

107 **Baseline characteristics**

108 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
109 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
110 deaths. The number of fetal deaths related to birth defects was 4,343, accounting for 10.0% of all fetal deaths. Baseline demographic
111 characteristics are summarized in Table 1.

113 **IMRs, by birth defect groups and subtypes**

114 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
115 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
116 common defects in infant deaths were chromosomal abnormality (0.69 per 10,000 live births, 10.1%) and musculoskeletal system
117 anomalies (0.65 per 10,000 live births, 9.6%). Among subtypes of birth defects, congenital diaphragmatic hernia (CDH) showed the
118 highest IMR at 0.43 per 10,000 live births (supplementary material). Among specified anomalies, lethal birth defects with the next
119 highest IMRs were Tetralogy of Fallot (TOF) and hypoplastic left heart syndrome (HLHS) (with IMRs of 0.28 and 0.27 per 10,000

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3 120 live births, respectively). Among chromosomal abnormalities, Down syndrome was the most common chromosomal abnormality with
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5 121 IMR of 0.27 per 10,000 live births (Table 3).
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9 10 11 123 **FMRs by birth defect groups and subtypes**

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14 124 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
15
16 125 group was chromosomal abnormality, accounting for 33.1% of fetal deaths related to birth defect, and its FMR was 4.46 per 10,000
17
18 126 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
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20 127 followed by other chromosomal abnormality, unspecified congenital heart malformation, and Edward syndrome, with FMR of 1.36,
21
22 128 0.93 and 0.82 per 10,000 total births, respectively (Table 3 and supplementary material).
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26 27 129 **IMRs and FMRs by birth defect groups, according to the maternal age group**

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30 130 In the analysis according to maternal age group, 2,529 live births, 113 fetal deaths not related to birth defects, and 12 fetal deaths
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32 131 related to birth defects were excluded due to missing values of maternal age. In infant deaths related to birth defect, anomaly of the
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34 132 circulatory system was most common in all age groups (Table 4, Figure 1). IMRs of chromosomal abnormality seemed to be increased
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36 133 in groups IV and V compared to that in group III. However, statistically significant difference was only observed between group V
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38 134 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
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3 135 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
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6 136 10,000 live births). In fetal deaths related to birth defect, most FMRs by birth defects were highest in the youngest group, except for
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8 137 FMR by chromosomal abnormality which was significantly higher in group V compared to that in group III (OR 7.01, 95% CI, 2.09-
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10 138 23.52) (Table 5, Figure 2). Compared to FMR of group II, FMRs of chromosomal abnormality were significantly higher in group IV
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12 139 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
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14 140 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).
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16 141 Individually, FMRs for anomalies of nervous system and cardiovascular system, and, other and unspecified anomalies were
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18 142 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,
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20 143 95% CI 2.52-27.67, respectively)
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28 145 **Discussion**

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31 146 It is important to know the types of severe birth defects which can lead fetal and infant deaths and their prevalence. Previously, the
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33 147 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-
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35 148 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].
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38 149 Although there might be methodological limitation and variations, the prenatal and postnatal detection rates of birth defects in live
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3 150 births seems increasing. In this study, 22.8% of infant deaths of Korea were related to birth defects. IMR and FMR caused by birth
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5 151 defects between 2009 and 2015 were 6.84 per 10,000 live births and 13.47 per 10,000 total births, respectively.
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8 152 The most common birth defect group related to infant deaths was anomaly of the circulatory system. However, the most common birth
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10 153 defect subtype was CDH. Despite advances in prenatal diagnosis and neonatal intensive care including extracorporeal membrane
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12 154 oxygenation and inhaled nitric oxide use, mortality rates due to CDH remain high, ranging from 50% to 70% with great variability
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15 155 between centers [15-17]. The second most common birth defect in infant deaths related to birth defect was TOF. The 10-year survival
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17 156 rate of TOF has been reported to be approximately 95 % [18, 19]. When we consider the prevalence of TOF in live births in Korea
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20 157 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
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22 158 nationwide infant survival rates of TOF in Korea will be approximately 93.3%, which is similar to survival rates in the other reports
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25 159 [18, 19].
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28 160 As expected, when IMRs and FMRs caused by birth defects were compared according to maternal age group, IMRs and FMRs due
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30 161 to chromosomal abnormality were higher in older maternal age groups (IV and V) compared to those in group II or III. FMRs due to
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32 162 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,
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34 163 95% CI: 1.77-6.78, respectively). FMR was much higher in group I. Especially, IMR and FMR due to anomalies of the nervous
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37 164 system were significantly higher in group I compared with those in group III, indicating higher prevalence of severe anomalies of
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39 165 nervous system in teenage pregnancies. In North America, fortification of flour and grain products became mandatory in 1998.
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3 166 Following folic acid fortification, prevalence of spina bifida birth in Canada fell by over 50% and that of other neural tube defects
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5 167 (NTDs) fell by approximately one-third [20]. In addition, the registry of ‘European surveillance of congenital anomalies’ has
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7 168 concluded that mandatory folic acid fortification is needed because the prevalence of NTDs has not decreased in Europe despite
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9 169 longstanding recommendations aiming at promoting periconceptional folic acid supplementation [21]. Results of Cochrane databases
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11 170 systematic review also showed a protective effect of daily folic acid supplementation in preventing NTDs compared to no
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13 171 intervention/placebo or vitamins and minerals without folic acid (risk ratio 0.31, 95% CI 0.17- 0.58); five studies; 6708 births; high
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15 172 quality evidence) [22]. Teenage pregnancies are more likely unplanned and exposed to alcohol, drug, sexual abuse, and nutritional
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17 173 imbalance. When pregnancies are complicated by birth defects in young age, they might be resulted in TOP, more easily. This study
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19 174 demonstrated increasing trends of IMRs and FMRs due to birth defects in the youngest and oldest maternal age groups. However, high
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21 175 IMRs and FMRs due to birth defects in the youngest age group were more pronounced except for chromosomal abnormality. It is
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23 176 known that adolescent pregnancy is associated with higher risks of adverse neonatal outcomes, such as low birth weight, preterm
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25 177 delivery [23]. In regard to birth defects, gastroschisis has been shown to be higher in young mothers [24, 25]. However, there has been
26
27 178 no other associations between young maternal age and any other birth defect, to our knowledge. Although it is unclear whether high
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29 179 IMRs and FMRs related to birth defects in the youngest maternal age group in this study are associated maternal age, or other social,
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31 180 nutritional, and environmental factors, further investigation might be needed in the future. In addition, mandatory folic acid
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33 181 fortification in Korea might help reduce nervous system anomalies because the youngest age group is less likely to take
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35 182 periconceptional folic acid supplementation and the overall prevalence of spina bifida in Korea shows increasing tendency [13].
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3 183 In Europe, increasing trend of trisomy 13, 18, and 21 between 1990 and 2009 was reported [9]. In Korea, most of prenatal screening
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5 184 methods are available, such as the first trimester combined test, Quad screening, integrated, sequential test and cell-free DNA
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8 185 screening [26]. However, the legally acceptable pregnancy termination is very restrictive in Korea. The maternal and child health law
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10 186 only permits an abortion for one of the following reasons; if the pregnant woman or her spouse suffers from an eugenic or hereditary
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12 187 mental or physical disease specified by presidential decree, if the woman or her spouse suffers from a communicable disease specified
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14 188 by presidential decree, if the pregnancy results from rape or incest or if continuation of the pregnancy is likely to jeopardize the
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16 189 mother's health. Therefore, it is almost impossible to estimate the proportions of TOP due to birth defects among fetal deaths. An
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18 190 international study has reported that the total mean prevalence of Down syndrome (in stillbirths, live births, and TOP) is increased
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20 191 from 13.1 to 18.2/10,000 births between 1993 and 2004 with increasing maternal age [27]. However, the total mean prevalence of
21
22 192 Down syndrome live births remains stable at 8.3/10,000 births, balanced by a great increase of TOP [27]. Maternal age at conception
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24 193 has been increased in Korea, although there are race/ethnic specific variations in birth defects [28]. IMR and FMR by Down syndrome
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26 194 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
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28 195 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
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30 196 approximately 93.6%. Based on the increased prevalence of Down syndrome in the international study, according to increasing
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32 197 maternal age [27], we can expect that TOP due to Down syndrome may be also considerable in Korea.
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34 198 The first limitation of this study is that death cause of fetal/infant deaths might be mostly made by clinician without autopsy. Although
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36 199 most autopsies performed in the Republic of Korea are forensic autopsies, the autopsy rates for total mortality and unusual death in
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3 200 Korea were reported as 2.4% and 18.1%, respectively, in 2015, which were very low [29, 30]. It could be related with the
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5 201 overwhelming majority of fetal losses due to unspecified nervous, cardiovascular, and other system. Because one or two disease
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7 202 codes are registered as the main code in death registry, multiple anomalies might have been included in one category. The second
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9 203 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
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11 204 comprehensive surveillance system with periodic production of data and monitoring to have effective prevention and management of
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13 205 birth defects. Lastly, this study did not include data on maternal nationality, paternal age, educational background, antenatal care, or
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15 206 parents' occupation due to high rates of missing values. However, this study is the first one that reports IMRs and FMRs caused by
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17 207 birth defects in Korea and different patterns according to maternal age group. Severe birth defects with high FMR were found to be
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19 208 more common in extreme maternal age groups (the youngest and the oldest). Except chromosomal abnormality, most severe
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21 209 anomalies, especially those of the nervous system and cardiovascular system, were more common in teenage pregnancies.
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27 210 As maternal age at conception is getting increased in Korea and screening tools are developing, prevalence and prenatal diagnosis of
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29 211 chromosomal abnormalities are likely to be increased. Multi-disciplinary cooperation among government, politician, clinicians, and
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31 212 non-governmental organization is urgent not only for increasing fertility rate, but also for increasing healthy pregnancies with effective
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33 213 prevention and management of birth defects, especially for extreme maternal age groups and for supporting complicated pregnancies.
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36 214 A mandatory folic acid fortification needs to be discussed and considered in Korea.
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3 216 **Author contributions**
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5 217 We confirm that all the authors have made substantive intellectual contributions to the paper; they understand their role in taking
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8 218 responsibility and being accountable for what is published. JCS conceptualized and reviewed the paper. HSK and DJK conceptualized
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10 219 the paper, gathered the results, analyzed the data and wrote the article. YHC, JHW, SKC, and IYP analyzed the data and reviewed the
11
12 220 paper. YGP performed statistical analysis of the data.
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18 222 **Funding**
19

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24 225 **Conflict of Interest**
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26 226 None declared.
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31 228 **Details of ethics approval**
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33 229 We obtained approval from the institutional review board of Catholic University of Korea (KC17ZESI0409).
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37 230 **Data sharing statement**
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40 231 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	Fetal deaths
				by birth defects	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.

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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.

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

Chromosomal birth defects	Total N. of cases	Proportion	Prevalence	N. of infant deaths	Proportion	Prevalence	N. of fetal deaths	Proportion	Prevalence
	caused by birth defect	(%) in birth defects	per 10000 total births	caused by birth defect	(%) in birth defects	per 10000 live births	caused by birth defect	(%) in birth defects	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
Klinefelter'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 abnormalities	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

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

Maternal age group	IMR									
	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)	
Birth defects (ICD-10)										
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.

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

Maternal age group	FMR									
	I (10-19 y)	OR (95% CI)	II (20-29 y)	OR (95% CI)	III (30-34 y)	OR (95% CI)	IV (35-39 y)	OR (95% CI)	V (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.

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

331 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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336 Figure 2. Fetal mortality caused by birth defects, according to maternal age group.

337 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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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).

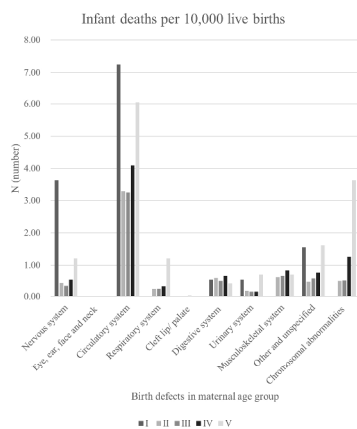


Figure 1. Infant mortality caused by birth defects, according to maternal age group.
 Maternal age groups: '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).

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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).

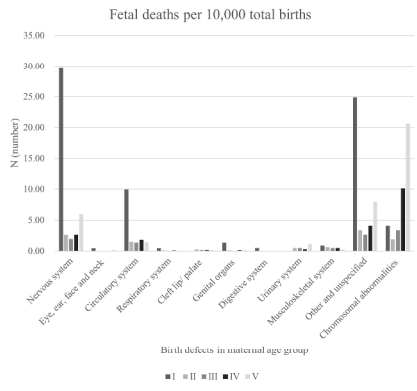


Figure 2. Fetal mortality caused by birth defects, according to maternal age group.
Maternal age groups: '10-19 yr' (I), '20-29 yr' (II), '30-34 yr' (III), '35-39 yr' (IV), and '40-55 yr' (V).

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Supplementary material.

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

	N. of infant deaths	Proportion	Prevalence	N. of fetal deaths	Proportion	Prevalence
Birth defects (ICD-10)	caused by	(%) in	per 10000	caused by	(%) in	per 10000
	birth defect	birth	livebirths	birth defect	birth	total births
	defects	defects		defects	defects	
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

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4	Mitral valve stenosis/insufficiency (Q23.2, 23.3)	8	0.37	0.03	0	0.00	0.00
5	Hypoplastic left heart syndrome (Q23.4)	86	3.95	0.27	7	0.16	0.02
6	Dextrocardia (Q 24.0)	0	0.00	0.00	3	0.07	0.01
7	Cor triatrium (Q 24.2)	2	0.09	0.01	0	0.00	0.00
8							
9	Subaortic stenosis (Q 24.4)	2	0.09	0.01	0	0.00	0.00
10							
11	Malformation of coronary vessels (Q24.5-24.6)	6	0.28	0.02	0	0.00	0.00
12							
13	Other heart malformation (Q24.2, 24.4-24.6)	88	4.04	0.28	50	1.15	0.16
14	Unspecified heart malformation (Q24.9)	75	3.45	0.24	299	6.88	0.93
15	Patent ductus arteriosus (Q25.0)*	87	4.00	0.27	0	0.00	0.00
16							
17	Coarctation/atresia/stenosis of aorta (Q25.1-25.3)	55	2.53	0.17	0	0.00	0.00
18							
19	Other malformations of aorta (Q25.4)	18	0.83	0.06	4	0.09	0.01
20							
21	Pulmonary artery atresia/stenosis (Q25.5, 25.6)	22	1.01	0.07	2	0.05	0.01
22							
23	Total anomalous pulmonary venous connection (Q26.2)	83	3.81	0.26	0	0.00	0.00
24	Partial anomalous pulmonary venous connection (Q26.3)	3	0.14	0.01	1	0.02	0.00
25	Peripheral arteriovenous malformation (Q27.3, 27.9, 27.9)	1	0.05	0.00	4	0.09	0.01
26							
27	Malformations of cerebral vessels (Q 28.2, 28.3)	6	0.28	0.02	4	0.09	0.01
28							
29	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
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32	Respiratory system (Q30-34)						
33	Other malformations of larynx, bronchus, trachea (Q31.0-32.4)	34	1.56	0.11	3	0.07	0.01
34							
35	Congenital cystic lung (Q33.0)	5	0.23	0.02	5	0.12	0.02
36							
37	Other malformation of lung (Q33.1-33.9)	42	1.93	0.13	16	0.37	0.05
38	Other malformations of respiratory system (Q34)	6	0.28	0.02	4	0.09	0.01
39							
40	Cleft lip/palate (Q35-37)	3	0.14	0.01	64	1.47	0.20
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42	Digestive system (Q38-45)						
43	Other malformation of mouths (Q38.5)	0	0.00	0.00	1	0.02	0.00
44							
45	Esophageal atresia/stenosis (Q39.0-39.2)	34	1.56	0.11	6	0.14	0.02
46	Malformation of upper elementary tract (Q40.0-40.9)	3	0.14	0.01	3	0.07	0.01
47							
48	Duodenal atresia/stenosis (Q41.0)	3	0.14	0.01	7	0.16	0.02
49							
50	Small intestine atresia/stenosis (Q41.1-41.9)	22	1.01	0.07	1	0.02	0.00
51							
52	Anorectal atresia/stenosis (Q42.0-42.3)	2	0.09	0.01	2	0.05	0.01
53							
54	Congenital megacolon (Q43.1)	44	2.02	0.14	0	0.00	0.00
55	Malrotation of colon (Q43.3)	9	0.41	0.03	0	0.00	0.00
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57	Persistent cloaca (Q43.7)	1	0.05	0.00	2	0.05	0.01
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4	Other intestinal and bile duct malformation (Q43.8-44.3)	42	1.93	0.13	6	0.14 0.02
5	Liver malformation (Q44.7)	4	0.18	0.01	0	0.00 0.00
6						
7	Other malformation of digestive system (Q 42.8, 43.0, 45.8, 45.9)	5	0.23	0.02	6	0.14 0.02
8						
9	Genital organs (Q50-56)	0	0.00	0.00	5	0.12 0.02
10						
11	Urinary system (Q60-64)					
12	Renal agenesis (Q60.0-60.6)	22	1.01	0.07	44	1.01 0.14
13	Autosomal recessive polycystic kidney (Q61.1)	10	0.46	0.03	6	0.14 0.02
14	Unspecified polycystic kidney (Q61.3)	6	0.28	0.02	23	0.53 0.07
15	Renal dysplasia (Q61.4)	6	0.28	0.02	30	0.69 0.09
16	Cystic kidney (Q61.0, Q61.5-61.9)	1	0.05	0.00	3	0.07 0.01
17	Congenital hydronephrosis (Q62.0-62.8)	2	0.09	0.01	14	0.32 0.04
18	Other renal anomaly (Q63.0, 63.2, 63.8, 63.9)	3	0.14	0.01	30	0.69 0.09
19	Posterior urethral valve (Q64.2)	3	0.14	0.01	3	0.07 0.01
20	Congenital absence of bladder and urethra (Q64.5-64.9)	1	0.05	0.00	6	0.14 0.02
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22	Musculoskeletal system (Q65-79)					
23						
24	Club foot-talipes equinovarus (66.0)	0	0.00	0.00	1	0.02 0.00
25	Other congenital feet deformities (Q66.1-66.9)	0	0.00	0.00	4	0.09 0.01
26	Congenital deformities of skull, face, and jaw (Q67.0-67.4)	0	0.00	0.00	2	0.05 0.01
27	Pectus carinatum (Q67.6)	2	0.09	0.01	0	0.00 0.00
28	Other congenital musculoskeletal deformities (Q68.0-Q70.9)	0	0.00	0.00	12	0.28 0.04
29	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
30	Other malformation of limbs and pelvic girdle (Q74.0-Q74.2, 74.8)	3	0.14	0.01	19	0.44 0.06
31	Arthrogryposis multiplex congenita (Q74.3)	4	0.18	0.01	1	0.02 0.00
32	Craniosynostosis (Q75.0)	6	0.28	0.02	0	0.00 0.00
33	Malformations of skull and face bones (Q75.1-75.9)	6	0.28	0.02	7	0.16 0.02
34	Klippel-Feil syndrome (Q76.1)	2	0.09	0.01	0	0.00 0.00
35	Malformations of spine and bony thorax (Q76.2-76.9)	2	0.09	0.01	7	0.16 0.02
36	Achondrogenesis/Hypochondrogenesis (Q77.0)	2	0.09	0.01	1	0.02 0.00
37	Thanatophoric dysplasia (Q77.1)	7	0.32	0.02	20	0.46 0.06
38	Asphyxiating thoracic dysplasia (Q77.2)	1	0.05	0.00	3	0.07 0.01
39	Achondroplasia/hypochondroplasia (Q77.4)	3	0.14	0.01	9	0.21 0.03
40	Osteogenesis imperfecta (Q78.0)	2	0.09	0.01	6	0.14 0.02
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4	Other osteochondrodysplasia (Q77.8, 78.8, 78.9)	2	0.09	0.01	4	0.09	0.01
5	Diaphragmatic hernia (Q79.0)	138	6.34	0.43	22	0.51	0.07
6	Other malformations of diaphragm (Q79.1)	6	0.28	0.02	1	0.02	0.00
7	Omphalocele (Q79.2)	10	0.46	0.03	15	0.35	0.05
8	Gastroschisis (Q79.3)	8	0.37	0.03	12	0.28	0.04
9	Prune belly syndrome (Q79.4)	0	0.00	0.00	3	0.07	0.01
10	Other musculoskeletal anomaly (Q79.8, 79.9)	4	0.18	0.01	19	0.44	0.06
11	Other and unspecified (Q80-89)	186	8.55	0.58	1105	25.44	3.43
12	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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4,5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	Not applicable

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7,8,9
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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.