

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	A national cohort study evaluating infant and fetal mortality caused by birth defects in Korea
<b>AUTHORS</b>	Ko, Hyun Sun; Kim, Dong Joo; Chung, Yoohyun; Wie, Jeong Ha; Choi, Sae Kyung; Park, In Yarg; Park, Yong Gyu; Shin, Jong Chul

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Vitaly Postoev International School of Public Health, Northern State Medical University, Russia
<b>REVIEW RETURNED</b>	15-Jun-2017

<b>GENERAL COMMENTS</b>	<p>Authors present fetal and infant mortality rates attributable to birth defects in Korea in 2009-2015. All rates are presented with stratification on groups of anomaly and maternal age. Although this topic is not new, there are not many papers presenting stratified rates, especially according to age of mother. However, some major revisions have to be done before making a decision about its acceptance.</p> <p>Major comments:</p> <ol style="list-style-type: none"><li>1. The source of data is official vital statistics, but routinely collected data can be inappropriate for epidemiological investigations sometimes and should be validated previously, especially in terms of causes of deaths. Was validity estimated, especially internal validity of causes of death? If so, it should be presented in Methods. If not, it should be done or at least mentioned as one of limitations.</li><li>2. In discussion you stated, that "death cause... is mostly made by clinician without autopsy". I consider, it is the first and the most important limitation of your study. It should be stated clearer in Methods to avoid misunderstanding and to explain high proportion of "unspecified malformation" in the table 3. Could it lead to overestimation of IMR and FMR due to birth defects somehow? Principles of diagnosing and proportion of autopsies according to gestational age might be presented also.</li><li>3. Prenatal screening policy in the country should be described as well as indications to the termination of pregnancy (because you stated, that "MOST of the terminations are illegal", not ALL).</li><li>4. More comparison of your results with published papers should be added in the Discussion part.</li></ol>
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	<p>Minor suggestions:</p> <ol style="list-style-type: none"> <li>1. I suggest to move table 3 to supplementary material or to remove it, since most of deaths are devoted to unspecified malformation.</li> <li>2. I suggest to include all odds ration (nor only statistically significant) in the tables 5, 6.</li> </ol>
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<b>REVIEWER</b>	<p>Waldemar A. Carlo  University of Alabama at Birmingham, Birmingham AL, United States of America  No Competing Interest</p>
<b>REVIEW RETURNED</b>	14-Aug-2017

<b>GENERAL COMMENTS</b>	<p>The sentence on lines 67 and 68 that "... birth defects occur during intrauterine life..." is poorly worded and should be clarified. I understand the intention. Maybe the sentence could be expressed better as "However, it is important to include stillbirths and abortions in addition to live births to account for all pregnancies with in birth defects."</p> <p>Details on the accuracy of the data on termination induced abortions should be addressed.</p> <p>It is unclear how complete the data on induced abortions are. I assume many abortions are included in the fetal deaths as fetuses with a trisomy are overrepresented in fetal deaths. However, a clear statement of the extent to which data on abortion were available is essential in the Methods. There is a mention of this in the Discussion but this is important in the Methods.</p> <p>For selective data, it would be important to know if the fetal loss was spontaneous or medically-induced. Otherwise, it is impossible to determine the path to mortality. It is important that some induced fetal deaths may not be for conditions that would be lethal during infancy, thus increasing the apparent incidence of congenital defects leading to deaths. I understand abortion is illegal in Korea so this is an important limitation to address in the Discussion as the data are likely to be biased.</p> <p>Table 1. Maternal age and gestational age are given with two decimal points. However, it is likely that the original data were reported most likely without a decimal point so the raw numbers are rounded down to full years or weeks. Thus, using decimal points will be misleading, resulting in underestimation of the real results. Given the large sample size, I think it is ok to include one decimal point but it is important to define in the methods whether or not the raw data for both fields included decimal points.</p> <p>It is unfortunate that data on the type of congenital heart disease is not specified in the overwhelming majority of fetal losses due to CHD. This is an important limitation that should be acknowledged.</p> <p>I could not find the data on congenital diaphragmatic hernia in Table 3.</p>
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	<p>The authors should reconsider the inclusion of PDA as a birth defect as more than 90% of their cases were in LBW infants in whom this is not really considered a congenital heart defect.</p> <p>The first paragraph addresses that the prevalence of birth defects appears to be increasing but they may want to specify that it may be the detection of birth defects that is increasing.</p> <p>The problem of lack of specific congenital heart disease is likely to lead to a bias in determining the specific birth defect subtypes prevalence. I think it is best to emphasize the limitation and to de-emphasize birth defect subtype analyses.</p> <p>The limitation of the accuracy of the data bases given that abortion data may be missing is important to address.</p> <p>There is no mention that the STROBE checklist was used.</p>
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### VERSION 1 – AUTHOR RESPONSE

#### Reviewer: 1

Reviewer Name: Vitaly Postoev

Institution and Country: International School of Public Health, Northern State Medical University, Russia

Competing Interests: None declared

Authors present fetal and infant mortality rates attributable to birth defects in Korea in 2009-2015. All rates are presented with stratification on groups of anomaly and maternal age. Although this topic is not new, there are not many papers presenting stratified rates, especially according to age of mother. However, some major revisions have to be done before making a decision about its acceptance.

Major comments:

1. The source of data is official vital statistics, but routinely collected data can be inappropriate for epidemiological investigations sometimes and should be validated previously, especially in terms of causes of deaths. Was validity estimated, especially internal validity of causes of death? If so, it should be presented in Methods. If not, it should be done or at least mentioned as one of limitations.

Response: Thank you for your valuable comment. We described it in the method section as follows. Since 2007, surveys and statistical analysis methods for infant and maternal death have been revised and complemented [14] to develop into a method for calculating more concrete, accurate numbers for fetal, infant, and maternal mortality rates in Korea. In summary, revision and supplementation of the statistics for fetal, infant and maternal death have been performed and validated by combination of official death registry data for vital statistics, survey data of public health center or medical institution, medical insurance claims database of the National Health Insurance Corporation on medical institutes across the country, and cremation reports data.

2. In discussion you stated, that "death cause... is mostly made by clinician without autopsy". I consider, it is the first and the most important limitation of your study. It should be stated clearer in Methods to avoid misunderstanding and to explain high proportion of "unspecified malformation" in the table 3. Could it lead to overestimation of IMR and FMR due to birth defects somehow? Principles of diagnosing and proportion of autopsies according to gestational age might be presented also.

Response: Thank you for your comment. We added a sentence 'However, data did not include information whether the cause of death was proven by autopsy.', in the method section.

And we added one more comment in the discussion section, as follows.

Although most autopsies performed in the Republic of Korea are forensic autopsies, the autopsy rates for total mortality and unusual death in Korea were reported as 2.4% and 18.1%, respectively, in 2015, which were very low [25, 26].

In addition, we changed this limitation as the first limitation.

3. Prenatal screening policy in the country should be described as well as indications to the termination of pregnancy (because you stated, that "MOST of the terminations are illegal", not ALL).

Response: Thank you for your comment. We added screening methods in Korea and indication of legal termination.

In Korea, most of prenatal screening methods are available, such as the first trimester combined test, Quad screening, integrated, sequential test and cell-free DNA screening.

However, the legally acceptable pregnancy termination is very restrictive in Korea. The maternal and child health law only permits an abortion for one of the following reasons; if the pregnant woman or her spouse suffers from an eugenic or hereditary mental or physical disease specified by Presidential Decree, if the woman or her spouse suffers from a communicable disease specified by Presidential Decree, if the pregnancy results from rape or incest or if continuation of the pregnancy is likely to jeopardize the mother's health.

3.1 In addition, we described that '759 fetal deaths (1.75% of all fetal deaths) recorded as 'termination of pregnancy' were excluded.', in method and results section

4. More comparison of your results with published papers should be added in the Discussion part.

Response: Thank you for your comments. We added more comparisons with data of other papers.

Minor suggestions:

1. I suggest to move table 3 to supplementary material or to remove it, since most of deaths are devoted to unspecified malformation.

Response: Thank you for your recommendation. We changed it.

2. I suggest to include all odds ration (nor only statistically significant) in the tables 5, 6.

Response: Thank you for your suggestion. However, non -significant data distracted significant odd ratios. We decided to describe significant odd ratios only in tables. If you still want to describe them, we will reconsider. Thank you.

**Reviewer: 2**

Reviewer Name: Waldemar A. Carlo

Institution and Country: University of Alabama at Birmingham, Birmingham AL, United States of America

Competing Interests: None

Comment: The sentence on lines 67 and 68 that "... birth defects occur during intrauterine life..." is poorly worded and should be clarified. I understand the intention. Maybe the sentence could be expressed better as "However, it is important to include stillbirths and abortions in addition to live births to account for all pregnancies with in birth defects."

Response: Thank you for your recommendation. We changed it.

Comment: Details on the accuracy of the data on termination induced abortions should be addressed.

Response: Thank you for your comments. We addressed it in the method and result section. It is unclear how complete the data on induced abortions are. I assume many abortions are included in the fetal deaths as fetuses with a trisomy are overrepresented in fetal deaths. However, a clear statement of the extent to which data on abortion were available is essential in the Methods. There is a mention of this in the Discussion but this is important in the Methods.

Thank you for your comments. We described that Fetal deaths recorded as 'termination of pregnancy (TOP)' were excluded in the method section. And we described that 759 fetal deaths (1.75% of all fetal deaths) recorded as 'TOP' were excluded. We addressed that there is no information whether fetal death was spontaneous or induced abortion, or termination of pregnancy, in the method section. And we added more comments about the limitation of data in the discussion section.

Comment: For selective data, it would be important to know if the fetal loss was spontaneous or medically-induced. Otherwise, it is impossible to determine the path to mortality. It is important that some induced fetal deaths may not be for conditions that would be lethal during infancy, thus increasing the apparent incidence of congenital defects leading to deaths. I understand abortion is illegal in Korea so this is an important limitation to address in the Discussion as the data are likely to be biased.

Response: Thank you for your comments.

We added the limitation of data including the legally acceptable pregnancy termination indications. However, the legally acceptable pregnancy termination is very restrictive in Korea. The maternal and child health law only permits an abortion for one of the following reasons; if the pregnant woman or her spouse suffers from an eugenic or hereditary mental or physical disease specified by Presidential Decree, if the woman or her spouse suffers from a communicable disease specified by Presidential Decree, if the pregnancy results from rape or incest or if continuation of the pregnancy is likely to jeopardize the mother's health.

Therefore, it is almost impossible to estimate the proportions of TOP due to birth defects among fetal deaths.

We agree that some induced fetal deaths may not be for conditions that would be lethal during infancy, thus increasing the apparent incidence of congenital defects leading to deaths. However, it is reality in Korea. Some parents choose induced abortion illegally when they find birth defect of fetus during pregnancy, due to non-medical reasons. A pregnant woman inducing her own miscarriage or any person performing an abortion is subject to imprisonment for one year or a fine. The penalties for medical personnel are increased to imprisonment for up to two years. Therefore, it is almost impossible to estimate the proportions of TOP due to birth defects among fetal deaths.

Comment: Table 1. Maternal age and gestational age are given with two decimal points. However, it is likely that the original data were reported most likely without a decimal point so the raw numbers are rounded down to full years or weeks. Thus, using decimal points will be misleading, resulting in underestimation of the real results. Given the large sample size, I think it is ok to include one decimal point but it is important to define in the methods whether or not the raw data for both fields included decimal points.

Response: Thank you for your comment. We include one decimal point in the maternal age and gestational age. And we described it in the methods.

Comment: It is unfortunate that data on the type of congenital heart disease is not specified in the overwhelming majority of fetal losses due to CHD. This is an important limitation that should be acknowledged.

Response: Thank you for your comment. We addressed it in the limitation section. I could not find the data on congenital diaphragmatic hernia in Table 3. Diaphragmatic hernia is included in the musculoskeletal system abnormality, in table 3.

Comment: The authors should reconsider the inclusion of PDA as a birth defect as more than 90% of their cases were in LBW infants in whom this is not really considered a congenital heart defect.

Response: Thank you for your comment. We would like to maintain original data, if it is possible, because we do not want to disrupt national data. Instead, we changed table 3 to supplementary material and we described that \*Patent ductus arteriosus cases included 81 cases whose birthweight was less than 2,500 g, in the bottom.

Comment: The first paragraph addresses that the prevalence of birth defects appears to be increasing but they may want to specify that it may be the detection of birth defects that is increasing.

Response: Thank you. We changed it.

Comment: Although there might be methodological limitation and variations, the prenatal and postnatal detection rates of birth defects in live births seems increasing. The problem of lack of specific congenital heart disease is likely to lead to a bias in determining the specific birth defect subtypes prevalence. I think it is best to emphasize the limitation and to de-emphasize birth defect subtype analyses.

Response: Thank you for your comment. We changed table 3 to supplemental data, based on your comment.

Comment: The limitation of the accuracy of the data bases given that abortion data may be missing is important to address.

Response: Thank you for comment. We described it in the discussion.

Comment: There is no mention that the STROBE checklist was used.

Response: Thank you. We mentioned that STROBE checklist was used.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Vitaly Postoev International School of Public Health, Northern State Medical University, Russia
<b>REVIEW RETURNED</b>	18-Sep-2017

<b>GENERAL COMMENTS</b>	1. I suggest to remove or change the phrase on lines 58-59: "However, it is important to include stillbirths and abortions in addition to live births to account for all pregnancies within birth defects", since it does not correspond with exclusion of TOPFAs cases. 2. The phrase "Fetal deaths recorded as 'termination of pregnancy (TOP)' were excluded" can be skipped in the Results section. It is enough to mentioned it in the discussion.
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<b>REVIEWER</b>	Waldemar A. Carlo University of Alabama at Birmingham- United States No Competing Interest
<b>REVIEW RETURNED</b>	15-Sep-2017

<b>GENERAL COMMENTS</b>	None.
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## VERSION 2 – AUTHOR RESPONSE

### Reviewer: 1

Reviewer Name: Vitaly Postoev

Institution and Country: International School of Public Health, Northern State Medical University, Russia

Please state any competing interests or state 'None declared': None declared

We stated as 'None declared'.

Comment 1. I suggest to remove or change the phrase on lines 58-59: "However, it is important to include stillbirths and abortions in addition to live births to account for all pregnancies within birth defects", since it does not correspond with exclusion of TOPFAs cases.

Response: Thank you for your suggestion. We changed it as follows: However, it is important to include stillbirths in addition to live births to account for all pregnancies within birth defects.

Comment 2. The phrase "Fetal deaths recorded as 'termination of pregnancy (TOP)' were excluded" can be skipped in the Results section. It is enough to mentioned it in the discussion.

Response: Thank you for your suggestion. We removed the phrase.

**Reviewer: 2**

Reviewer Name: Waldemar A. Carlo

Institution and Country: University of Alabama at Birmingham- United States

Competing Interests: None

Comment: None.

Response: Thank you again for your time and kind suggestions.

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 Shin1\*