Nationwide Increase in Cryptorchidism After the Fukushima Nuclear Accident

Kaori Murase, Joe Murase, Koji Machidori, Kentaro Mizuno, Yutaro Hayashi, and Kenjiro Kohri

OBJECTIVE To estimate the change of discharge rate after cryptorchidism surgery between pre- and postdisaster in Japan. Cryptorchidism cannot be diagnosed before birth and is not a factor that would influence a woman's decision to seek an abortion. Therefore, this disease is considered suitable for assessing how the Great East Japan Earthquake and the subsequent Fukushima Daiichi nuclear accident (2011) influenced congenital diseases.

MATERIALS AND METHODS We obtained cryptorchidism discharge data collected over 6 years from hospitals that were included in an impact assessment survey of the Diagnosis Procedure Combination survey database in Japan and used these data to estimate the discharge rate after cryptorchidism surgery before and after the disaster. The 94 hospitals in Japan that participated in Diagnosis Procedure Combination system and had 10 or more discharges after cryptorchidism surgery within successive 6 years covering pre- and postdisaster period (FY2010-FY2015) were involved. The change in discharge rate between pre- and postdisaster was analyzed using a Bayesian generalized linear mixed model.

RESULTS Nationwide, a 13.4% (95% credible interval 4.7%-23.0%) increase in discharge rates was estimated. The results of all sensitivity analyses were similar to the reported main results.

CONCLUSION The discharge rate of cryptorchidism was increased nationwide. The rates of low-weight babies or preterm births, risk factors of cryptorchidism, were almost constant during the study period, and age distribution of the surgery was also not changed, which suggested that the other factors that associated with the disaster increased the incidence of cryptorchidism. UROLOGY 118: 65–70, 2018. © 2018 Elsevier Inc.

After the Great East Japan Earthquake that occurred in 2011 and subsequent atomic disaster of the Fukushima Daiichi nuclear power plant, several articles have been published about the health impact. However, those studies reported the diseases associated with the accident, such as thyroid cancer in children from Fukushima Prefecture,[1,2] chronic diseases,[3] and psychological problems[4]; these studies were limited to a particular locality. To our knowledge, an exhaustive analysis has not been performed to determine the health status of people living in Japan after the disaster.

Cryptorchidism is one of the most frequent congenital abnormalities in pediatric urology disease.[5] Certain congenital diseases, such as Down syndrome or other trisomy syndromes, can be detected using noninvasive prenatal testing[6] or maternal serum screening[7]; however, prenatal screening is not available for cryptorchidism. Therefore, this disease does not influence whether pregnancies are continued to term, which increases the suitability of using cryptorchidism when assessing the influence of the nuclear accident on congenital diseases because the disease would not be underestimated because of abortions. Additionally, the relatively high frequency of cryptorchidism compared with other congenital diseases increases the stability of the estimation results.

A straightforward comparison between disaster-affected area and nonaffected area seemed to be difficult because many residents migrated from the affected area unlike usual natural disasters. Then, we will show nationwide increase in cryptorchidism. For this purpose, we obtained summarized discharge (ie, inpatient only) data[8] from an impact assessment survey of the Diagnosis Procedure Combination system[9,10] (DPC survey) published by the Ministry of Health, Labour and Welfare in Japan and subjected these data to our analyses. In Japan, there are no financial or opportunity-based barriers to medical care access because an "infant health checkup" is mandated by law, and the

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From Nagoya City University Graduate School of Natural Sciences, Nagoya, Japan; Goshawk Protection Fund, Tochigi, Japan; Machidori Clinic, Tokyo, Japan; the Department of Pediatric Urology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; and the Department of Nephro-Urology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Address correspondence to: Kaori Murase, Ph.D., Nagoya City University Graduate School of Natural Sciences, 1, Yamanohata, Mizuho-cho, Mizuho-ku, Nagoya 467-8501, Japan. E-mail: kmurase@nsc.nagoya-cu.ac.jp

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surgical cost of cryptorchidism is covered by universal public health-care system with the aid of a medical expense subsidy for children. Moreover, the surgical operation for the treatment of cryptorchidism is only required once for nearly all cases. Therefore, the discharge number in the DPC data reflects the actual number of surgeries in Japan well.

MATERIALS AND METHODS

Data Source

We obtained study approval from the institutional review board of Nagoya City University. Owing to the anonymous nature of the DPC survey data, the board waived the requirement for informed consent. The DPC data are announced every year. However, the announced data do not contain information that enables us to assess the increase and decrease tendency or fluctuation in the number of the surgical cases for each hospital for multiple years. In this study, for assessing such properties, we compiled the announced data for multiple years by hospital and by prefecture.

Data on the hospitals involved in the DPC survey are shown in Supplementary Table S1. During the investigation period, the DPC survey included approximately 20%-40% hospitals in Japan. All 80 academic hospitals were involved in the survey.[11] Many other public or private hospitals with the ability to perform cryptorchidism surgery also participated in the DPC survey. To protect personal information, hospitals that presented less than 10 cases of cryptorchidism are not included in the officially published DPC survey statistics. Therefore, only the hospitals for which the number of discharges after cryptorchidism surgery were available (ie, 10 cases or more) over the entire period were included, and the cases were then aggregated by year and by prefecture. We compiled 8-year (FY2008-FY2015), 7-year (FY2009-FY2015), 6-year (FY2010-FY2015), 5-year (FY2011-FY2015), 4-year (FY2012-FY2015), 3-year (FY2013-FY2015), and 2-year (FY2014-FY2015) data.

Demographic Information

Low-level fetal exposure to androgens is one of the causes of cryptorchidism, which is associated with low-weight babies or preterm births.[5] The rate of late childbearing may also concern the cryptorchidism. Thus, we examined those figures from the Ministry of Health, Labour and Welfare of Japan during the period of this study. The age distribution represented in the DPC survey data was also examined.

In Japan, all local governments are obligated by law to carry out infant health checkups in 1.5-3 year-old toddlers. Moreover, additional infant health checkups are also performed in infants who are less than a year old. Most cases of suspected cryptorchidism are identified during these checkups; thus, the consultation rate can affect the number of cryptorchidism surgeries performed. Therefore, we also examined the consultation rate of infant health checkups.

Secondarily Undescended Testes (UDT)

Trapped testes after inguinal hernia surgery were considered to be a potential factor that could influence the number of cryptorchidism surgeries. In Japan, 1.2% of pediatric inguinal hernia surgeries resulted in the trapped testes.[12] We extracted information on the number of inguinal hernia surgeries in children <15 years old from the 2010-2015 DPC data, and calculated the potential number of trapped testes cases. Regarding the number of trapped testes cases and cryptorchidism surgeries, we calculated the differences from the average of FY2010-FY2011 data to obtain the proportion of the increase in the number of trapped testes cases relative to the increase in the number of cryptorchidism surgeries.

Total Discharge Rate of the Selected Hospitals

To obtain the discharge rate for the selected hospitals, we totaled the annual number of cases for the selected hospitals and divided the values by the total population of the prefectures where the selected hospitals were located. Then, the 95% confidence intervals (CIs) were calculated under the assumption that the discharge number followed a Poisson distribution. The 6-year and the 8-year data were employed because the 6-year data had the largest number of discharges among the data that included pre- and postaccident years and the 8-year data had greatest number of preaccident discharge information, although the total numbers were not large. However, in FY2010, the number of discharges was multiplied by 4/3 because only 9 months of data were available for that year, and in FY2008 and 2009, the number was multiplied by 2 because only 6 months of data were available. Additionally, the total population in Japan was based on the statistics of the Basic Resident Registers, which showed the rate of foreigner registrations surged in 2013 as a result of a revision of the Basic Resident Registration Act.[13] Therefore, we subtracted the number pertaining to the sudden increase in foreigner registrations from the total population in Japan in 2013 and in 2014 to remove the apparent population increase.

Statistical Analysis

We used the 6-year data. The change in discharge rate between pre- and postdisaster was analyzed using a generalized linear mixed model (GLMM) with a log link function. Considering that the data might violate the Poisson assumption, we performed Poisson GLMM and a negative binomial GLMM analyses to determine the appropriate distribution for the data. The baseline and change in discharge rate of each prefecture were included as random effects (ie, random intercept and random slope model). The population of each prefecture in each year and the surveillance period of each year were considered as offset terms; therefore, we used the raw numbers of the surgery without any transformation regarding the surveillance period. To assess the goodness-of-fit of the models, we employed the "aods3" package of R. We then performed a Bayesian analysis using the appropriate distribution (see Supplementary Appendix S1 for details).

The study further included several sensitivity analyses to test the robustness of the main result. We performed the same analysis using the 8-year data.

RESULTS

Demographic Information

The incidence of cryptorchidism at 1 year of age is 1.0%-1.7% according to the Japanese guideline.[12] As there are about 500,000 births of male infants in Japan every year, 5000-8500 surgeries are expected to be required each year.

The rates of low-weight babies or preterm births in Japan were almost constant from 2008 to 2015 (Supplementary Table S2). The rate of late childbearing increased, but it occurred slowly throughout the investigation period (Supplementary Table S2). The age distributions of the

discharges after cryptorchidism surgery in the DPC survey participant hospitals were not altered during the same period (Supplementary Table S3). The consultation rates of the infant health checkups increased gradually, but this increase was very small (Supplementary Table S4).

Secondarily UDT

The increase in the number of the trapped testes cases relative to the average FY2010-FY2011 data estimated from the number of inguinal hernia surgeries was 14-39. These figures accounted for only 0.9%-3.4% of the increase in the number of cryptorchidism surgeries (Supplementary Table S5).

Total Discharge Number After Cryptorchidism Surgery

We showed the variation trend in the total discharge number after cryptorchidism surgery in the hospitals that had 10 or more discharges within successive years (Fig. 1, Supplementary Appendix S2-S8, data provided by year and by prefecture; and Supplementary Appendix S9, number of discharges and names of associated hospitals). The increase between FY2011 and FY2012 is obvious (Fig. 1A-D), and a gradual increase is observed from FY2012 to FY2014 (Fig. 1C-F).

In 94 hospitals in 35 prefectures, the number of discharges after cryptorchidism surgery was available over the entire period (6 years from FY2010 to FY2015) (Supplementary Appendix S4). The number covered 35%-40% of all the cryptorchidism surgeries in FY2010. The discharge rates between FY2010-FY2011 and FY2012-FY2015 showed distinct changes, and increases were maintained in FY2012-FY2015 (Fig. 2A). Regarding the 8-year data from FY2008 to FY2015 (40 hospitals in 25 prefectures, Supplementary Appendix S2), the number of the discharges in the preaccident 4-year period was stable (the number covered 18%-30% of all the cryptorchidism surgeries in FY2008), and the rates before and after the accident were different (Fig. 2B).

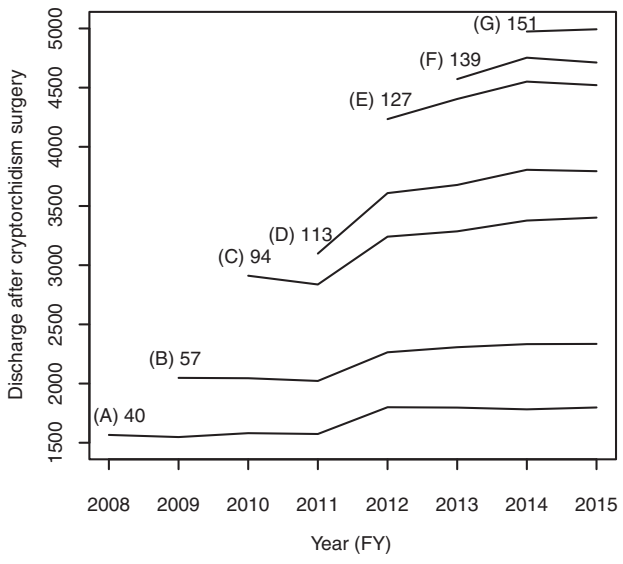

Figure 1. Cryptorchidism surgery discharges in Japan. The total number of discharges after cryptorchidism surgery in the selected hospitals that had 10 or more discharges over the entire period are presented. **(A)** FY2008-FY2015 (8 years). **(B)** FY2009-FY2015 (7 years). **(C)** FY2010-FY2015 (6 years). **(D)** FY2011-FY2015 (5 years). **(E)** FY2012-FY2015 (4 years). **(F)** FY2013-FY2015 (3 years). **(G)** FY2014-FY2015 (2 years). The number located at the left of each line plot indicates the number of selected hospitals.

Increase in the Discharge Rate

The goodness-of-fit test indicated that the negative binomial GLMM fitted the data well (χ^2 = 185.7, df = 205, P = .83), while the Poisson GLMM did not (χ^2 = 341.5, df = 206, P <.01). Thus, the negative binomial GLMM was considered to be more appropriate for the data used in this study. The result of the Bayesian negative binomial GLMM analysis for 6-year data is presented in Figure 3. Nationwide, a 13.4% increase (95% CI: 4.7%-23.0%, Fig. 3) was observed. Regarding the 8-year data, a 12.7% increase (95% CI: 2.1%-24.4%, Supplementary Fig. S1) was estimated. This result is similar to that of the 6-year data, and the rate of increase was stable. The results of all sensitivity analyses were similar to the reported main results (Supplementary Figs. S2 and S3).

Additionally, when we converted the discharge number of all age groups to those under the age of 3 using the age distribution published as part of the DPC survey (Supplementary Table S3 and Supplementary Appendix S10 and S11), we obtained a 16.9% increase (95% CI: 2.9%-32.4%, Supplementary Fig. S4). The age distribution was calculated using all hospitals in the survey. Thus, the distribution was not necessarily applied to each hospital in our analysis, which suggests that the results from patients under the age of 3 might not be reliable (although they are noteworthy).

DISCUSSION

Both the Bayesian GLMM analysis results for 6-year and 8-year data showed that the increased rate of discharge after cryptorchidism surgery in all age groups after the nuclear accident was estimated at about 13%. The sensitivity analyses also showed similar results. When the discharge numbers are converted to represent the rate for patients under the age of 3, the increased rate of discharge was 16.9%.

Low-level fetal exposure to androgens is one of the causes of cryptorchidism, which is associated with low-weight babies or preterm births.[5] However, the rates of low-weight babies or preterm births in Japan were almost constant from 2008 to 2015. The rate of late childbearing and the consultation rate of the obligatory infant health checkup increased, but these increase occurred very slowly throughout the investigation period. In addition, the contribution of the estimated number of cases of trapped testes after inguinal hernia surgery to the number of cryptorchidism

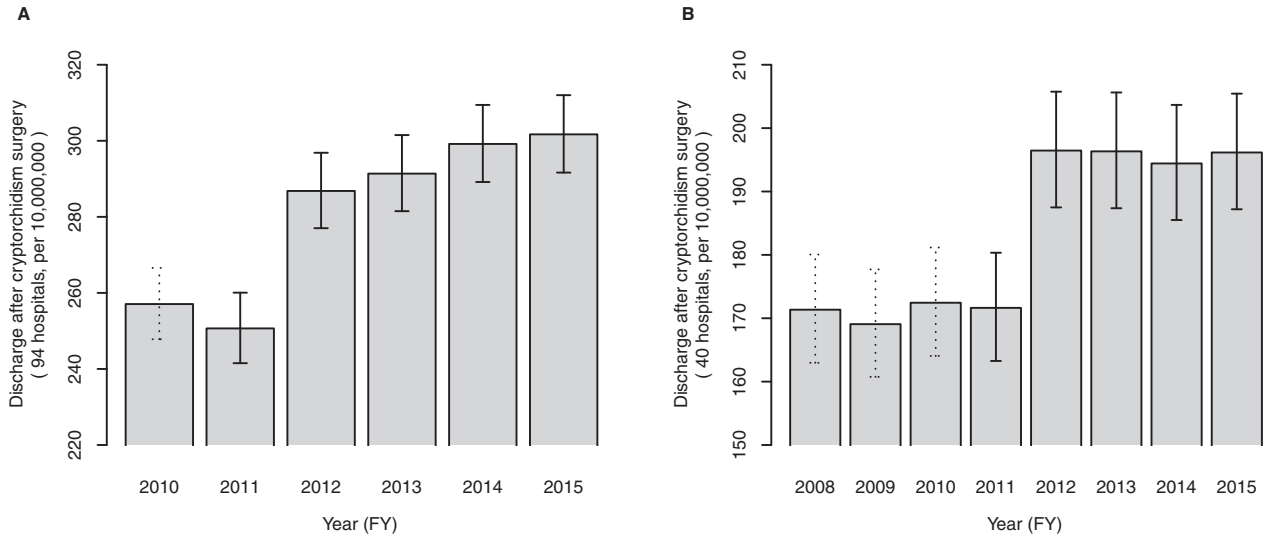

Figure 2. Discharge rate after cryptorchidism surgery (6-year and 8-year data). The number of discharges after cryptorchidism surgery (per 10 million persons) are presented. **(A)** FY2010-FY2015 (total cases from 94 hospitals). **(B)** FY2008-FY2015 (total cases from 40 hospitals). In FY2010, the number of discharges is multiplied by 4/3 because only 9 months of data were available for that year, and in FY2008 and FY2009, the number is multiplied by 2 because only 6 months of data were available. The discharge number was assumed to follow a Poisson distribution; thus, 95% CIs are also displayed. The CIs in FY2008, FY2009, and FY2010 are displayed with dotted lines because they are based on the multiplied numbers. CI, confidence interval.

surgeries was also small. Therefore, the possibility that these factors were involved was small.

The surgical operation for the treatment of cryptorchidism is only required once for nearly all cases, and patients under 3 years of age consistently covered about 64% of total discharge; thus, the increase in the discharge rate would primarily be attributed to newborn cryptorchidism patients rather than patients greater than 3 years of age. There have been no major changes in the diagnosis and treatment of cryptorchidism since the Japanese guidelines were published in 2005, and during the study period, the policy described in the guidelines was considered to be implemented throughout Japan. Even though health-care consolidation may have occurred in the hospitals included in the DPC[14] because of the reform of local public hospitals,[15] the sudden increase between FY2011 and FY2012 cannot be explained by such issues related to diagnosis and treatment or health-care consolidation.

Considering the massiveness of the earthquake and subsequent nuclear accident, emotional stress and radioactive material would be considered as 2 main possible factors contributing to the increase. However, in human no association has been observed between cryptorchidism and severe emotional stress (maternal bereavement due to the death of a close relative[16]), although prenatal maternal stress has proved to be a risk factor for cryptorchidism in rats. In contrast, radioactive material released from the Fukushima nuclear accident may be concerned considering its amount[17] and known toxicity.[18] After the nuclear accident, radionuclides may have been distributed through the ecosystem through food contamination[19,20] and the incineration of debris as part of the treatment of disaster waste[21,22] (35%-40% of radiocesium in the debris was emitted in a certain cites). Recently, the use of the contaminated soil (lower than 8000 bq/kg) for public works nationwide has been proposed by the Ministry of Environment,[23] which could result in the further spread of radionuclides. However, this is a matter of concern due to the potential unknown effects associated with radionuclides. Of course, we should also examine other factors such as maternal overweight and obesity,[24] analgesics during pregnancy,[25] smoking, herbicides, pesticides, and endocrine-disrupting chemicals.[26] In any case, the etiology of the increase in cryptorchidism is unknown. Along with these factors, the number of cryptorchidism surgeries, which included the surgeries for secondarily UDT, was also included in our analysis, which makes it difficult to draw a clear interpretation of the results. Further research is expected.

CONCLUSION

The discharges after cryptorchidism surgery were increased nationwide after the Great East Japan Earthquake in 2011 and subsequent nuclear accidents. The rates of low-weight babies or preterm births, risk factors for cryptorchidism, were almost constant during the study period. The distribution of patient age during surgery and the consultation rate of infant health checkups also did not change. Moreover, the increase in the cryptorchidism surgery due to trapped testes after inguinal hernia surgery was considered to be very small. These suggested that the other factors increased the incidence of cryptorchidism. Emotional stress due to catastrophic events might be concerned, but a report said that severe maternal emotional

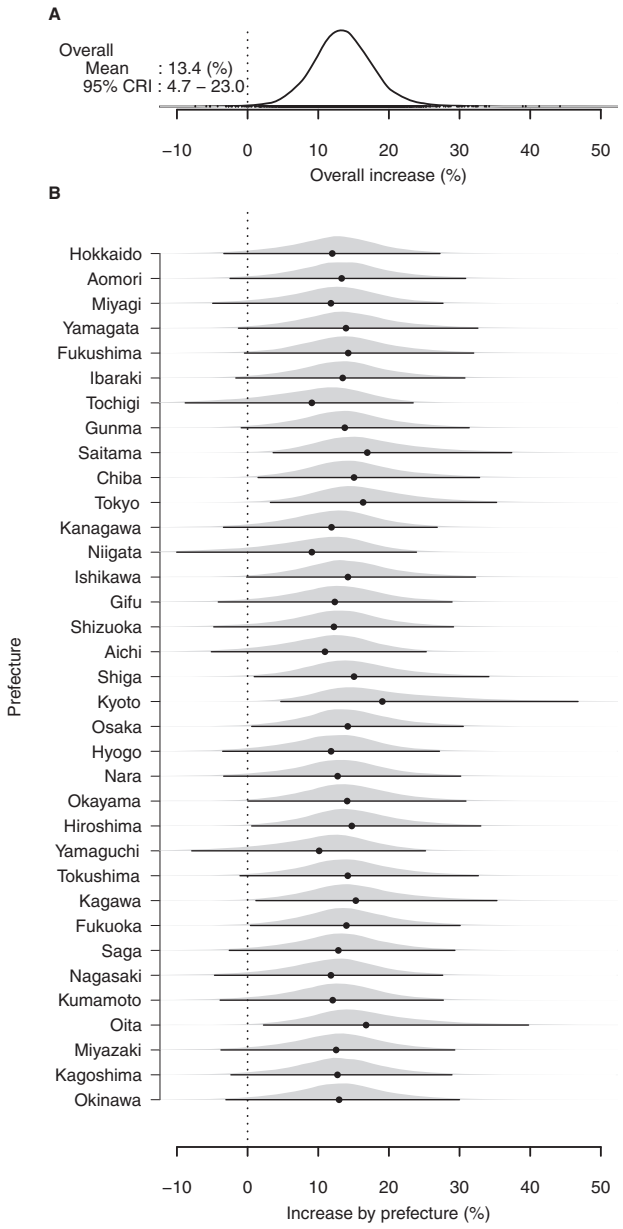

Figure 3. Increase in the rate of discharge after cryptorchidism surgery after the nuclear accident (6-year data). Posterior distributions of the percent increase in the rate of discharge after cryptorchidism surgery are presented. **(A)** Overall mean. **(B)** Each prefecture. The filled circles indicate the posterior mean values, and the horizontal bars indicate the 95% credible intervals.

stress did not affect the incidence of cryptorchidism. A large amount of radionuclides emitted from the Fukushima was suspected to be a major cause but currently no evidence is available.

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APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urology.2018.04.033.